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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/44, 31/445, 31/535, 31/54, C07D 211/56, 273/01, 279/12, 285/15

A1

(11) International Publication Number: **WO 96/14844**

(43) International Publication Date: 23 May 1996 (23.05.96)

(21) International Application Number: PCT/US95/14812

(22) International Filing Date: 13 November 1995 (13.11.95)

(30) Priority Data:

339,607	15 November 1994 (15.11.94)	US
468,120	6 June 1995 (06.06.95)	US

(60) Parent Applications or Grants
(63) Related by Continuation

US	339,607 (CIP)
Filed on	15 November 1994 (15.11.94)
US	468,120 (CIP)
Filed on	6 June 1995 (06.06.95)

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(81) Designated States: AL, AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: CYCLIC AMIDINE ANALOGS AS INHIBITORS OF NITRIC OXIDE SYNTHASE

(57) Abstract

Disclosed herein are the heterocyclic compounds and pharmaceutically acceptable salts thereof which have been found to be useful in the treatment of nitric oxide synthase mediated diseases and disorders.

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TITLE OF THE INVENTION

CYCLIC AMIDINE ANALOGS AS INHIBITORS OF NITRIC OXIDE SYNTHASE

BACKGROUND OF THE INVENTION

This application is directed to inhibitors of Nitric oxide synthase, and in particular cyclic amidines.

Nitric Oxide in Biology.

The emergence of nitric oxide (NO), a reactive, inorganic radical gas as a molecule contributing to important physiological and pathological processes is one of the major biological revelations of recent times. This molecule is produced under a variety of physiological and pathological conditions by cells mediating vital biological functions. Examples include endothelial cells lining the blood vessels; nitric oxide derived from these cells relaxes smooth muscle and regulates blood pressure and has significant effects on the function of circulating blood cells such as platelets and neutrophils as well as on smooth muscle, both of the blood vessels and also of other organs such as the airways. In the brain and elsewhere nitric oxide serves as a neurotransmitter in non-adrenergic non-cholinergic neurons. In these instances nitric oxide appears to be produced in small amounts on an intermittent basis in response to various endogenous molecular signals. In the immune system nitric oxide can be synthesized in much larger amounts on a protracted basis. Its production is induced by exogenous or endogenous inflammatory stimuli, notably endotoxin and cytokines elaborated by cells of the host defense system in response to infectious and inflammatory stimuli. This induced production results in prolonged nitric oxide release which contributes both to host defense processes such as the killing of bacteria and viruses as well as pathology associated with acute and chronic inflammation in a wide variety of diseases. The discovery that nitric oxide production is mediated by a unique series of three closely related enzymes, named nitric oxide synthases, which utilize

the amino acid arginine and molecular oxygen as co-substrates has provided an understanding of the biochemistry of this molecule and provides distinct pharmacological targets for the inhibition of the synthesis of this mediator, which should provide significant beneficial effects in a wide variety of diseases.

Nitric Oxide Synthases

Nitric oxide and L-citrulline are formed from L-arginine via the dioxygenase activity of specific nitric oxide synthases (NOSs) in mammalian cells. In this reaction, L-arginine, O_2 and NADPH are cosubstrates while FMN, FAD and tetrahydrobiopterin are cofactors. NOSs fall into two distinct classes, constitutive NOS (cNOS) and inducible NOS (iNOS) . Two constitutive NOSs have been identified. They are:

(i) a constitutive, Ca^{++}/calmodulin dependent enzyme, located in the endothelium (ecNOS or NOS 3), that releases NO in response to receptor or physical stimulation,

(ii) a constitutive, Ca^{++}/calmodulin dependent enzyme, located in the brain (ncNOS or NOS 1) and elsewhere, that releases NO in response to receptor or physical stimulation,

The third isoform identified is inducible NOS (iNOS or NOS 2):

(iii) a Ca^{++} independent enzyme which is induced after activation of vascular smooth muscle, macrophages, endothelial cells, and a large number of other cells by endotoxin and cytokines. Once expressed, this inducible NO synthase produces NO in relatively large amounts for long periods of time.

Spectral studies of both the mouse macrophage iNOS and rat brain ncNOS have shown that these enzymes (which has been classified as P-450-like enzymes from their CO-difference spectra) contain a heme moiety. The structural similarity between NOS and the P-

450/flavoprotein complex suggests that the NOS reaction mechanism may be similar to P-450 hydroxylation and/or peroxidation. This indicates that NOS belongs to a class of flavohemeproteins which contain both heme and flavin binding regions within a single protein in contrast to the multiprotein NADPH oxidase or Cytochrome P-450/NADPH Cyt c reductase complexes.

Distinct Functions of NO Produced by Different Nitric Oxide Synthases.

The NO released by the constitutive enzymes (NOS 1 and NOS 3) acts as an autocoid mediating a number of physiological responses. Two distinct cDNAs accounting for the activity of NOS 1 and NOS 3 in man have been cloned, one for NOS 1 (Nakane *et. al., FEBS Letters, 316*, 175-182, 1993) which is present in the brain and a number of peripheral tissues, the other for an enzyme present in endothelium (NOS 3) (Marsden *et. al., FEBS Letters, 307*, 287-293, 1992). This latter enzyme is critical for production of NO to maintain vasorelaxation. A second class of enzyme, iNOS or NOS 2, has been cloned from human liver (Geller *et. al., PNAS, 90*, 3491-5, 1993), and identified in more than a dozen other cells and tissues, including smooth muscle cells, chondrocytes, the kidney and airways. As with its counterpart from the murine macrophage, this enzyme is induced upon exposure to cytokines such as gamma interferon (IFN-γ), interleukin-1β (IL-1β), tumor necrosis factor (TNF-α) and LPS (lipopolysaccharide). Once induced, iNOS expression continues over a prolonged period of time. The enzyme does not require exogenous calmodulin for activity.

Endothelium derived relaxation factor (EDRF) has been shown to be produced by NOS 3 (Moncada *et. al., Pharmacol. Reviews, 43*, 109-142, 1991). Studies with substrate analog inhibitors of NOS have shown a role for NO in regulating blood pressure in animals and blood flow in man, a function attributed to NOS 3. NO has also been shown to be an effector of the cytotoxic effects of activated macrophages (Nathan, *FASEB J., 6*, 3051-64, 1992) for fighting tumour cells and invading microorganisms (Wright *et al., Card. Res., 26* ,48-57, 1992 and

Moncada *et al.*, *Pharmacological Review*, *43*, 109-142, 1991). It also appears that the adverse effects of excess NO production, in particular pathological vasodilation and tissue damage, may result largely from the effects of NO synthesized by the NOS 2.

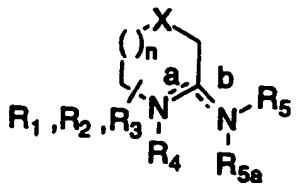
NO generated by NOS 2 has been implicated in the pathogenesis of inflammatory diseases. In experimental animals hypotension induced by LPS or TNF-α can be reversed by NOS inhibitors and reinitiated by L-arginine (Kilbourn *et. al.*, *PNAS*, *87*, 3629-32, 1990). Conditions which lead to cytokine-induced hypotension include septic shock, hemodialysis (Beasley and Brenner, *Kidney Int.*, *42*, Suppl., *38*, S96--S100, 1992) and IL-2 therapy in cancer patients (Hibbs *et. al.*, *J. Clin. Invest.*, *89*, 867-77, 1992). NOS 2 is implicated in these responses, and thus the possibility exists that a NOS inhibitor would be effective in ameliorating cytokine-induced hypotension. Recent studies in animal models have suggested a role for NO in the pathogenesis of inflammation and pain and NOS inhibitors have been shown to have beneficial effects on some aspects of the inflammation and tissue changes seen in models of inflammatory bowel disease, (Miller *et. al.*, *J. Pharmacol. Exp. Ther.*, *264*, 11-16, 1990) and cerebral ischemia and arthritis (Ialenti *et. al.*, *Br. J. Pharmacol .*, *110*, 701-6, 1993; Stevanovic-Racic *et al.*, *Arth. & Rheum.*, *37*, 1062-9, 1994). Moreover transgenic mice deficient in NOS 1 show diminished cerebral ischemia (Huang *et. al.*, *Science*, *265*, 1883-5, 1994).

Further conditions where there is an advantage in inhibiting NO production from L-arginine include therapy with cytokines such as TNF, IL-1 and IL-2 or therapy with cytokine-inducing agents, for example 5, 6-dimethylxanthenone acetic acid, and as an adjuvant to short term immunosuppression in transplant therapy. In addition, compounds which inhibit NO synthesis may be of use in reducing the NO concentration in patients suffering from inflammatory conditions in which an excess of NO contributes to the pathophysiology of the condition, for example adult respiratory distress syndrome (ARDS) and myocarditis.

There is also evidence that an NO synthase enzyme may be involved in the degeneration of cartilage which takes place in autoimmune and/or inflammatory conditions such as arthritis, rheumatoid arthritis, chronic bowel disease and systemic lupus erythematosis (SLE). It is also thought that an NO synthase enzyme may be involved in insulin- dependent diabetes mellitus. Therefore, a yet further aspect of the present invention provides cyclic amidine derivatives or salts thereof in the manufacture of a medicament for use in cytokine or cytokine-inducing therapy, as an adjuvant to short term immunosuppression in transplant therapy, for the treatment of patients suffering from inflammatory conditions in which an excess of NO contributes to the pathophysiology of the condition.

SUMMARY OF THE INVENTION

The invention disclosed herein encompasses compounds of Formula I



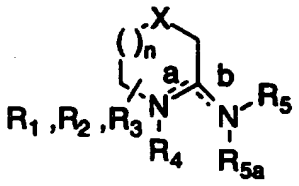
I

and pharmaceutically acceptable salts thereof which have been found useful in the treatment of nitric oxide synthase mediated diseases and disorders, including neurodegenerative disorders, disorders of gastrointestinal motility and inflammation. These diseases and disorders include hypotension, septic shock, toxic shock syndrome, hemodialysis related conditions, tuberculosis, cancer, IL-2 therapy such as in cancer patients, cachexia, immunosuppression such as in transplant therapy, autoimmune and/or inflammatory indications including sunburn, eczema or psoriasis and respiratory conditions such as bronchitis, asthma, oxidant-induced lung injury and acute respiratory distress (ARDS),

glomerulonephritis, restenosis, inflammatory sequelae of viral infections, myocarditis, heart failure, atherosclerosis, osteoarthritis, rheumatoid arthritis, septic arthritis, chronic or inflammatory bowel disease, ulcerative colitis, Crohn's disease, systemic lupus erythematosis (SLE), ocular conditions such as ocular hypertension, retinitis and uveitis, type 1 diabetes, insulin-dependent diabetes mellitus and cystic fibrosis. Compounds of Formula I are also usful in the treatment of hypoxia, hyperbaric oxygen convulsions and toxicity, dementia, Alzheimer's disease, Sydenham's chorea, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis, epilepsy, Korsakoff's disease, imbecility related to cerebral vessel disorder, NO mediated cerebral trauma and related sequelae, ischemic brain edema (stroke), sleeping disorders, eating disorders such as anorexia, schizophrenia, depression, pre-menstrual syndrome (PMS), urinary incontinence, anxiety, drug and alcohol addiction, pain, migraine, emesis, immune complex disease, as immunosupressive agents, acute allograft rejection, infections caused by invasive microorganisms which produce NO and for preventing or reversing tolerance to opiates and diazepines.

DETAILED DESCRIPTION OF THE INVENTION

The invention disclosed herein encompasses compounds of Formula I



I

and pharmaceutically acceptable salts thereof wherein
side a or side b has a double bond,
n is 0, 1, 2, 3 or 4
X is selected from CH_2, O, S and NH,

R_1, R_2 and R_3 are each independently selected from the group consisting of

(a) hydrogen,
(b) C_{1-12}alkoxy,
(c) C_{1-12}alkylS(O)$_k$ wherein k is 0, 1 or 2,
(d) mono C_{1-12}alkylamino,
(e) (di-C_{1-12}alkyl)amino,
(f) C_{1-12}alkylcarbonyl,
(g) C_{1-12}alkyl,
(h) C_{2-12}alkenyl,
(i) C_{2-12}alkynyl,
(j) C_{5-10}cycloalkyl,
(k) hetero C_{5-10}cycloalkyl,wherein the hetero C_{5-10}cycloalkyl optionally contains 1 or 2 heteroatoms selected from S, O and N,
(l) aryl, selected from phenyl or naphthyl,
(m) heteroaryl, wherein heteroaryl is selected from the group consisting of:
    (1) benzimidazolyl,
    (2) benzofuranyl,
    (3) benzooxazolyl,
    (4) furanyl,
    (5) imidazolyl,
    (6) indolyl,
    (7) isooxazolyl,
    (8) isothiazolyl,
    (9) oxadiazolyl,
    (10) oxazolyl,
    (11) pyrazinyl,
    (12) pyrazolyl,
    (13) pyridyl,
    (14) pyrimidyl,
    (15) pyrrolyl,
    (17) isoquinolyl,

(18) tetrazolyl,
(19) thiadiazolyl,
(20) thiazolyl,
(21) thienyl, and
(22) triazolyl,

(n) amino,
(o) oxo,
(p) C(O)OH,
(q) $C(O)OR_6$, R_6 is selected from hydrogen, phenyl, cyclohexyl or C_{1-6}alkyl,

each of (b) to (m) being optionally mono or di- substituted the substituents being independently selected from
(1) hydroxy,
(2) carboxy,
(3) $-NR_6R_7$, where R_7 is selected from hydrogen, phenyl, cyclohexyl or C_{1-6}alkyl,
(4) $-OR_6$,
(5) $-C(O)OR_6$,
(6) $-S(O)_kR_6$,
(7) halo selected from F, Cl, Br and I,
(8) $-C(=NR_6)-NHR_7$,
(9)-S-$C(=NR_6)-NHR_7$,

or when two members of the group R_1, R_2 and R_3, including the optional substituents present thereon, reside on the same atom of Formula I, or two of the group R_1, R_2 and R_3, including the optional substituents present thereon, reside on adjacent atoms of Formula I, said two members may optionally be joined, such that together with the atoms to which they are attached there is formed a saturated or unsaturated monocyclic ring of 5, 6 or 7 atoms, said monocyclic ring optionally containing up to three hetero atoms selected from N, O or S,

or when a member of the group R_1, R_2 and R_3 including the optional substituents present thereon, resides on an atom

adjacent to the N on which R_4 resides, said member may optionally be joined with R_4, such that together with the N on which R_4 resides and the carbon on which said member resides there is formed a saturated or unsaturated monocyclic heterocycle of 5, 6 or 7 atoms, said monocycle optionally containing up to three hetero atoms selected from N, O or S,

R_4, R_5 and R_{5a} are each independently selected from the group consisting of

(a) hydrogen,

(b) linear and branched C_{1-12}alkyl, optionally mono or di-substituted, the substituents being independently selected from

(1) hydroxy,
(2) carboxy,
(3) $-NR_6R_7$,
(4) $-OR_6$,
(5) $-C(O)OR_6$,
(6) $-S(O)_kR_6$,
(7) halo selected from F, Cl, Br and I,
(8) phenyl, optionally mono or di-substituted with hydroxy, halo, C_{1-4}alkyl, or C_{1-4}alkoxy,

(c) $-C(O)NR_8R_9$, where R_8 and R_9 are each independently hydrogen, phenyl, cyclohexyl or C_{1-6}alkyl, said C_{1-6}alkyl optionally substituted by

(1) hydroxy,
(2) amino,
(3) carboxy,
(4) $-NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently H, C_{1-6}alkyl, phenyl or benzyl,
(5) $-OR_{10}$,
(6) $-C(O)OR_{10}$,
(7) $-S(O)_mR_{10}$, where m is 0, 1 or 2,
(8) halo selected from F, Cl, Br and I,

(9) optionally substituted aryl wherein aryl and aryl substituents are as defined above,

(10) optionally substituted heteroaryl wherein heteroaryl and heteroaryl substituents are as defined above,

(11) optionally substituted C5-10cycloalkyl wherein cycloalkyl and cycloalkyl substituents are as defined above,

(12) optionally substituted hetero C5-10cycloalkyl wherein hetero cycloalkyl and hetero cycloalkyl substituents are as defined above,

(d) -C(S)NR8R9,

(e) -C(O)R9,

(f) -C(O)OR9,

(g) -C(S)R9,

(h) phenyl,

(i) cyclohexyl,

provided that R4 is present only when side a is a single bond and R5a is present only when side b is a single bond.

Within this embodiment is the genus wherein

n is 0, 1, 2, 3 or 4,

X is selected from CH_2, O, S and NH,

R_1, R_2 and R_3 are each independently selected from the group consisting of

(a) hydrogen,

(b) C1-6alkoxy,

(c) C1-6alkylamino,

(d) C1-6alkylcarbonyl,

(e) C1-6alkyl,

(f) C2-6alkenyl,

(g) C5, C6 or C7cycloalkyl,

(h) hetero C5 or C6 cycloalkyl,wherein the hetero C5 or C6 cycloalkyl optionally contains 1 heteroatom selected from S, O and N,

(i) aryl, selected from phenyl or naphthyl,

(j) heteroaryl, wherein heteroaryl is selected from the group consisting of:

(1) furanyl,
(2) pyrazinyl,
(3) pyrazolyl,
(4) pyridyl,
(5) pyrimidyl,
(6) thiazolyl,
(7) thienyl, and
(8) triazolyl,

each of (b) to (j) being optionally mono or di- substituted the substituents being independently selected from

(1) hydroxy,
(2) carboxy,
(3) $-NR_6R_7$, where R_6 and R_7 are each independently hydrogen, phenyl or C_{1-4}alkyl,
(4) $-OR_6$,
(5) $-C(O)OR_6$,
(6) $-S(O)_kR_6$, where k is 0, 1 or 2,
(7) halo selected from F, Cl, Br and I,

or when two members of the group R_1, R_2 and R_3 including the optional substituents present thereon, reside on the same atom of Formula I, or two of the group R_1, R_2 and R_3, including the optional substituents present thereon, reside on adjacent atoms of Formula I, said two members may optionally be joined, such that together with the atoms to which they are attached there is formed a saturated or unsaturated monocyclic ring of 5, 6 or 7 atoms, said monocyclic ring optionally containing up to three hetero atoms selected from N, O or S,

or when a member of the group R_1, R_2 and R_3 including the optional substituents present thereon, resides on an atom adjacent to the N on which R_4 resides, said member may optionally be joined with R_4, such that together with the N

on which R4 resides and the carbon on which said member resides there is formed a saturated or unsaturated monocyclic heterocycle of 5, 6 or 7 atoms, said monocycle optionally containing up to three hetero atoms selected from N, O or S,

R4, R5 and R5a are each independently selected from the group consisting of

(a) hydrogen,

(b) linear and branched C_{1-6}alkyl, optionally mono or di-substituted, the substituents being independently selected from

(1) hydroxy,
(2) carboxy,
(3) $-NR_6R_7$,
(4) $-OR_6$,
(5) $-C(O)OR_6$,
(6) $-S(O)_kR_6$, where k is 0, 1 or 2,
(7) halo selected from F, Cl, Br and I,

(c) $-C(O)NR_8R_9$, where R8 and R9 are each independently hydrogen, phenyl, cyclohexyl or C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted by

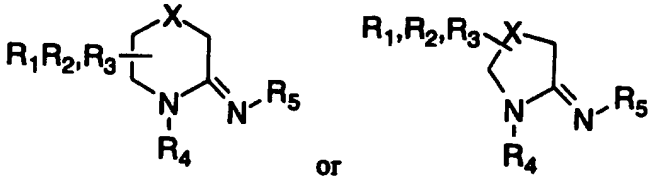
(1) hydroxy,
(2) amino,
(3) carboxy,
(4) $-NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently H, C_{1-4}alkyl, phenyl or benzyl,
(5) $-OR_{10}$,
(6) $-C(O)OR_{10}$,
(7) $-S(O)_mR_{10}$, where m is 0, 1 or 2,
(8) halo selected from F, Cl, Br and I,
(9 optionally substituted aryl wherein the aryl and substituents are as defined above,
(10) optionally substituted heteroaryl wherein the heteroaryl and substituents are as defined above,

(11) optionally substituted C_5 or C_6 cycloalkyl wherein the cycloalkyl and substituents are as defined above,
(12) optionally substituted hetero C_5 or C_6 cycloalkyl wherein the hetero cycloalkyl and substituents are as defined above,

(d) $-C(S)NR_8R_9$,
(e) $-C(O)R_9$,
(f) $-C(O)OR_9$,
(g) $-C(S)R_9$,
(h) phenyl,
(i) cyclohexyl,

such that R_4 is present only when side a is a single bond and side b is a double bond.

Within this genus is the class of compounds of the formulae



wherein
X is selected from CH_2, S and NH,
R_1, R_2 and R_3 are each independently selected from the group consisting of

(a) hydrogen,
(b) linear and branched C_{1-4}alkyl, said C_{1-4}alkyl being optionally mono or di- substituted the substituents being independently selected from
(1) carboxy,
(2) $-NR_6R_7$, wherein R_6 and R_7 are each independently hydrogen or C_{1-3}alkyl,
(3) $-OR_6$,
(4) $-C(O)OR_6$,
(5) $-S(O)_kR_6$, where k is 0, 1 or 2,

R_4 is selected from the group consisting of

(a) hydrogen,

(b) -C(O)NHR9, where R9 is hydrogen or C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted by

(1) hydroxy,

(2) amino,

(3) carboxy,

(4) $-NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently

C_{1-3}alkyl,

(5) $-OR_{10}$,

(6) $-C(O)OR_{10}$,

(7) $-S(O)_mR_{10}$, where m is 1 or 2,

(8) halo selected from F, Cl, Br and I,

(c) -C(S)NHR9;

(d) C_{1-3}alkyl;

R_5 is selected from the group consisting of

(a) hydrogen,

(b) -C(O)NHR9,

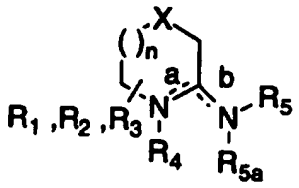
(c) -C(S)NR8R9.

(d) C_{1-3}alkyl.

As appreciated by those of skill in the art the additional carbon members of the Formula I ring, "$(\ )_n$" and definitions "CH_2" and "NH" under X, provide available positions for the substituents R_1, R_2 or R_3.

When any variable (e.g. R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, Ra, k, n, p etc.) occurs in any position of a compound of Formula I, its definition on each occurrence is independent of its definition at every other occurrence.

Accordingly, in one aspect the invention disclosed herein encompasses compounds of Formula I



I

and pharmaceutically acceptable salts thereof wherein
side a or side b has a double bond,
n is 0, 1, 2, 3 or 4
X is selected from CH_2, $CR_{12}R_{13}$, O, $S(O)_m$, NH, and -N(C_{1-6}alkyl)-,
m is 0, 1 or 2,
R_1, R_2, R_3, R_{12} and R_{13} are each independently selected from the group consisting of

(a) hydrogen,
(b) C_{1-12}alkoxy,
(c) C_{1-12}alkyl$S(O)_k$ wherein k is 0, 1 or 2,
(d) mono C_{1-12}alkylamino,
(e) (di-C_{1-12}alkyl)amino,
(f) C_{1-12}alkylcarbonyl,
(g) C_{1-12}alkyl,
(h) C_{2-12}alkenyl,
(i) C_{2-12}alkynyl,
(j) C_{5-10}cycloalkyl,
(k) hetero C_{5-10}cycloalkyl,wherein the hetero C_{5-10}cycloalkyl optionally contains 1 or 2 heteroatoms selected from S, O and N,
(l) aryl, selected from phenyl or naphthyl,
(m) heteroaryl, wherein heteroaryl is selected from the group consisting of:
    (1) benzimidazolyl,
    (2) benzofuranyl,
    (3) benzooxazolyl,
    (4) furanyl,
    (5) imidazolyl,

(6) indolyl,
(7) isooxazolyl,
(8) isothiazolyl,
(9) oxadiazolyl,
(10) oxazolyl,
(11) pyrazinyl,
(12) pyrazolyl,
(13) pyridyl,
(14) pyrimidyl,
(15) pyrrolyl,
(17) isoquinolyl,
(18) tetrazolyl,
(19) thiadiazolyl,
(20) thiazolyl,
(21) thienyl, and
(22) triazolyl,

(n) amino,
(o) oxo,
(p) C(O)OH,
(q) $C(O)OR_6$, R_6 is selected from hydrogen, phenyl, cyclohexyl or C_{1-6}alkyl,

each of (b) to (m) being optionally mono or di- substituted the substituents being independently selected from

(1) hydroxy,
(2) carboxy,
(3) $-NR_6R_7$, where R_7 is selected from hydrogen, phenyl, cyclohexyl or C_{1-6}alkyl,
(4) $-OR_6$,
(5) $-C(O)OR_6$,
(6) $-S(O)_kR_6$,
(7) halo selected from F, Cl, Br and I,
(8) $-C(=NR_6)-NHR_7$,
(9)-S-$C(=NR_6)-NHR_7$,

or when two members of the group R_1, R_2 and R_3 including the optional substituents present thereon, reside on the same carbon atom of Formula I, or two of the group R_1, R_2 and R_3, including the optional substituents present thereon, reside on adjacent atoms of Formula I, said two members may optionally be joined, such that together with the atom to which they are attached there is formed a saturated or unsaturated monocyclic ring of 5, 6 or 7 atoms, said monocyclic ring optionally containing up to three hetero atoms selected from N, O or S,

or when a member of the group R_1, R_2 and R_3 including the optional substituents present thereon, resides on an atom adjacent to the N on which R_4 resides, said member may optionally be joined with R_4, such that together with the N on which R_4 resides and the carbon on which said member resides there is formed a saturated or unsaturated monocyclic heterocycle of 5, 6 or 7 atoms, said monocycle optionally containing up to three hetero atoms selected from N, O or S,

with the proviso that one of R_{12} and R_{13} is other than hydrogen,

R_4, R_5 and R_{5a} are each independently selected from the group consisting of

(a) hydrogen,

(b) linear and branched C_{1-12}alkyl, optionally mono or di-substituted, the substituents being independently selected from

(1) hydroxy,
(2) carboxy,
(3) $-NR_6R_7$,
(4) $-OR_6$,
(5) $-C(O)OR_6$,
(6) $-S(O)_kR_6$,
(7) halo selected from F, Cl, Br and I,

(8) phenyl, optionally mono or di-substituted with hydroxy, halo, C_{1-4}alkyl, or C_{1-4}alkoxy,

(c) -C(O)NR8R9, where R8 and R9 are each independently hydrogen, phenyl, cyclohexyl or C_{1-6}alkyl, said C_{1-6}alkyl optionally substituted by

(1) hydroxy,

(2) amino,

(3) carboxy,

(4) -$NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently H, C_{1-6}alkyl, phenyl or benzyl,

(5) -OR_{10},

(6) -$C(O)OR_{10}$,

(7) -$S(O)_mR_{10}$, where m is 0, 1 or 2,

(8) halo selected from F, Cl, Br and I,

(9) optionally substituted aryl wherein aryl and aryl substituents are as defined above,

(10) optionally substituted heteroaryl wherein heteroaryl and heteroaryl substituents are as defined above,

(11) optionally substituted C5-10cycloalkyl wherein cycloalkyl and cycloalkyl substituents are as defined above,

(12) optionally substituted hetero C_{5-10}cycloalkyl wherein hetero cycloalkyl and hetero cycloalkyl substituents are as defined above,

(d) -C(S)NR8R9,

(e) -COR9,

(f) -C(O)OR9,

(g) -C(S)R9,

(h) phenyl,

(i) cyclohexyl,

provided that R4 is present only when side a is a single bond and R5a is present only when side b is a single bond.

Within this embodiment is the genus wherein

m is 0, 1 or 2,

n is 0, 1, 2, 3 or 4,
X is selected from CH_2, $CR_{12}R_{13}$, O, $S(O)_m$ NH, and -N(C_{1-6}alkyl)-,
R_1, R_2, R_3, R_{12} and R_{13} are each independently selected from the group consisting of

(a) hydrogen,
(b) C_{1-6}alkoxy,
(c) C_{1-6}alkylamino,
(d) C_{1-6}alkylcarbonyl,
(e) C_{1-6}alkyl,
(f) C_{2-6}alkenyl,
(g) C_5, C_6 or C_7cycloalkyl,
(h) hetero C_5 or C_6 cycloalkyl,wherein the hetero C_5 or C_6 cycloalkyl optionally contains 1 heteroatom selected from S, O and N,
(i) aryl, selected from phenyl or naphthyl,
(j) heteroaryl, wherein heteroaryl is selected from the group consisting of:
    (1) furanyl,
    (2) pyrazinyl,
    (3) pyrazolyl,
    (4) pyridyl,
    (5) pyrimidyl,
    (6) thiazolyl,
    (7) thienyl, and
    (8) triazolyl,

each of (b) to (j) being optionally mono or di- substituted the substituents being independently selected from
(1) hydroxy,
(2) carboxy,
(3) -NR_6R_7, where R_6 and R_7 are each independently hydrogen, phenyl or C_{1-4}alkyl,
(4) -OR_6,
(5) -$C(O)OR_6$,
(6) -$S(O)_kR_6$, where k is 0, 1 or 2,

(7) halo selected from F, Cl, Br and I,

or when two members of the group R_1, R_2 and R_3 including the optional substituents present thereon, reside on the same atom of Formula I, or two of the group R_1, R_2 and R_3, including the optional substituents present thereon, reside on adjacent atoms of Formula I, said two members may optionally be joined, such that together with the atoms to which they are attached there is formed a saturated or unsaturated monocyclic ring of 5, 6 or 7 atoms, said monocyclic ring optionally containing up to three hetero atoms selected from N, O or S,

or when a member of the group R_1, R_2 and R_3 including the optional substituents present thereon, resides on an atom adjacent to the N on which R_4 resides, said member may optionally be joined with R_4, such that together with the N on which R_4 resides and the carbon on which said member resides there is formed a saturated or unsaturated monocyclic heterocycle of 5, 6 or 7 atoms, said monocycle optionally containing up to three hetero atoms selected from N, O or S,

with the proviso that one of R_{12} and R_{13} is other than hydrogen,

R_4, R_5 and R_{5a} are each independently selected from the group consisting of

(a) hydrogen,

(b) linear and branched C_{1-6}alkyl, optionally mono or di-substituted, the substituents being independently selected from

(1) hydroxy,

(2) carboxy,

(3) $-NR_6R_7$,

(4) $-OR_6$,

(5) $-C(O)OR_6$,

(6) $-S(O)_kR_6$, where k is 0, 1 or 2,

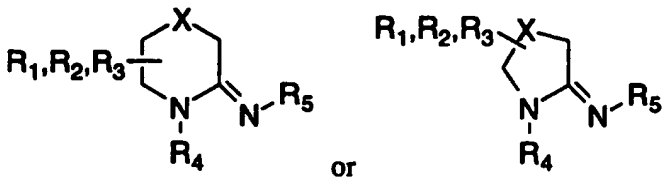
(7) halo selected from F, Cl, Br and I,

(c) -C(O)NR8R9, where R8 and R9 are each independently hydrogen, phenyl, cyclohexyl or C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted by
(1) hydroxy,
(2) amino,
(3) carboxy,
(4) -$NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently H, C_{1-4}alkyl, phenyl or benzyl,
(5) -OR_{10},
(6) -$C(O)OR_{10}$,
(7) -$S(O)_mR_{10}$, where m is 0, 1 or 2,
(8) halo selected from F, Cl, Br and I,
(9) optionally substituted aryl wherein the aryl and substituents are as defined above,
(10) optionally substituted heteroaryl wherein the heteroaryl and substituents are as defined above,
(11) optionally substituted C_5 or C_6 cycloalkyl wherein the cycloalkyl and substituents are as defined above,
(12) optionally substituted hetero C_5 or C_6 cycloalkyl wherein the hetero cycloalkyl and substituents are as defined above,

(d) -C(S)NR8R9,
(e) -COR9,
(f) -C(O)OR9,
(g) -C(S)R9,
(h) phenyl,
(i) cyclohexyl,

such that R4 is present only when side a is a single bond and side b is a double bond.

Within this genus is the class of compounds of the formulae



wherein

X is selected from $CR_{12}R_{13}$, $S(O)_m$ and -N(C_{1-4}alkyl)-,

R_1,R_2, R_3, R_{12} and R_{13} are each selected from the group consisting of

(a) hydrogen,

(b) hydroxy,

(c) linear and branched C_{1-4}alkyl or linear and branched C_{1-4}alkoxy, wherein said C_{1-4}alkyl or C_{1-4}alkoxy is optionally mono or di- substituted the substituents being independently selected from

(1) carboxy,

(2) -NR_6R_7, wherein R_6 and R_7 are each independently hydrogen or C_{1-3}alkyl,

(3) -OR_6,

(4) -$C(O)OR_6$,

(5) -$S(O)_kR_6$, where k is 0, 1 or 2,

with the proviso that one of R_{12} and R_{13} is other than hydrogen,

R_4 is selected from the group consisting of

(a) hydrogen,

(b) -C(O)NHR9, where R9 is hydrogen or C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted by

(1) hydroxy,

(2) amino,

(3) carboxy,

(4) -$NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently

C_{1-3}alkyl,

(5) -OR_{10},

(6) -$C(O)OR_{10}$,

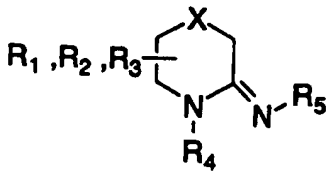
(7) -$S(O)_mR_{10}$, where m is 1 or 2,

(8) halo selected from F, Cl, Br and I,

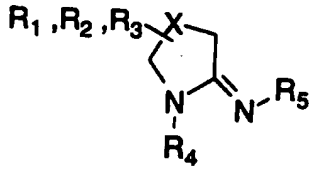
(c) -C(S)NHR9;
(d) C1-3alkyl;

R5 is selected from the group consisting of
(a) hydrogen,
(b) -C(O)NHR9,
(c) -C(S)NR8R9.
(d) C1-3alkyl.

In an alternative embodiment the invnetion is directed to compounds of the formulae



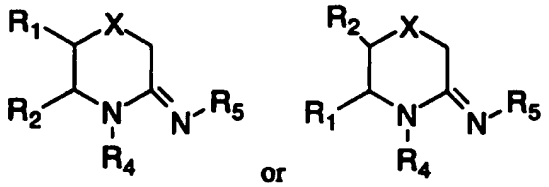
or



wherein
X is -N(C1-3alkyl)-,
R1, R2 and R3 are each independently selected from the group consisting of
(a) hydrogen,
(b) linear and branched C1-4alkyl, said C1-4alkyl being optionally mono or di- substituted the substituents being independently selected from
(1) carboxy,
(2) -NHR7, wherein R6 and R7 are each independently hydrogen or C1-3alkyl,
(3) -C(O)OR6, and
(4) -S(O)kR6, where k is 1 or 2,
(c) hydroxy,
R4 is selected from the group consisting of
(a) hydrogen,
(b) C1-3alkyl;
R5 is selected from the group consisting of

(a) hydrogen,
(b) -C(O)NHR9, where R9 is hydrogen or C1-4alkyl, said C1-4alkyl optionally substituted by
(1) hydroxy,
(2) amino,
(3) carboxy,
(4) -NR10R11, wherein R10 and R11 are each independently C1-3alkyl,
(5) -OR10,
(6) -C(O)OR10,
(7) -SR10, and
(8) -S(O)mR10, where m is 1 or 2,
(9) halo selected from F, Cl, Br and I,
(c) -C(S)NR8R9.
(d) C1-3alkyl;

Within this embodiment is the genus of compound of the formulae



wherein
X is -N(C1-3alkyl)-,
R1 and R2 are each selected from
hydrogen or linear and branched C1-4alkyl, said C1-4alkyl being optionally mono or di- substituted the substituents being independently selected from
(1) carboxy,
(2) -NHR7, wherein R6 and R7 are each independently hydrogen or C1-3alkyl,

(3) -C(O)OR6, and

(4) -S(O)kR6, where k is 1 or 2,

R4 is selected from the group consisting of

(a) hydrogen,

(b) C1-3alkyl;

R5 is selected from the group consisting of

(a) hydrogen,

(b) -C(O)NHR9, where R9 is hydrogen or C1-4alkyl, said C1-4alkyl optionally substituted by

(1) hydroxy,

(2) amino,

(3) carboxy,

(4) -NR10R11, wherein R10 and R11 are each independently C1-3alkyl,

(5) -OR10,

(6) -C(O)OR10,

(7) -SR10, and

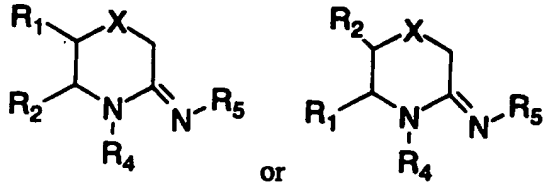
(8) -S(O)mR10, where m is 1 or 2,

(9) halo selected from F, Cl, Br and I,

(c) -CSNR8R9.

(d) C1-3alkyl.

Within this genus are the compounds of the formulae



or

wherein

X is -N(C1-3alkyl)-,

R1 is selected from the group consisting of

hydrogen, hydroxy or linear and branched C1-4alkyl, said C1-4alkyl

being optionally mono or di- substituted the substituents being independently selected from

(1) carboxy,

(2) -NHR7, wherein R6 and R7 are each independently hydrogen or C1-3alkyl,

(3) -C(O)OR6, and

(4) -S(O)kR6, where k is 1 or 2,

R2 is linear and branched C1-4alkyl,

R4 is selected from the group consisting of

(a) hydrogen,

(b) C1-3alkyl;

R5 is selected from the group consisting of

(a) hydrogen,

(b) -C(O)NHR9, where R9 is hydrogen or C1-4alkyl, said C1-4alkyl optionally substituted by

(1) hydroxy,

(2) amino,

(3) carboxy,

(4) -NR10R11, wherein R10 and R11 are each independently

C1-3alkyl,

(5) -OR10,

(6) -C(O)OR10,

(7) -SR10, and

(8) -S(O)mR10, where m is 1 or 2,

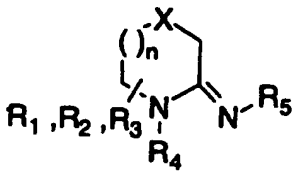
(9) halo selected from F, Cl, Br and I,

(c) -CSNR8R9.

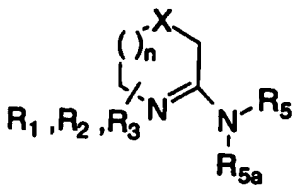
(d) C1-3alkyl.

Exemplifying the invention are the compounds of Examples 1 through 161.

As appreciated by those of skill in the art, compounds of Formula I include those wherein there is a double bond at side a or b such as those shown in Formula Ia or Ib or tautomeric forms thereof:

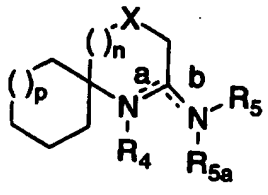


Ia

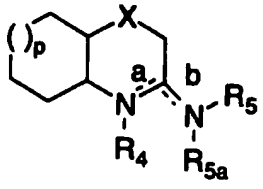


Ib

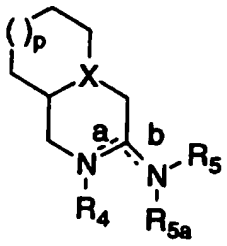
As also appreciated by those of skill in the art, compounds of Formula 1 wherein or when two members of the group R_1, R_2 and R_3 are joined together to form a ring are intended to include such formulae as:



or

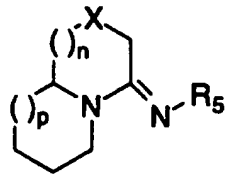


or



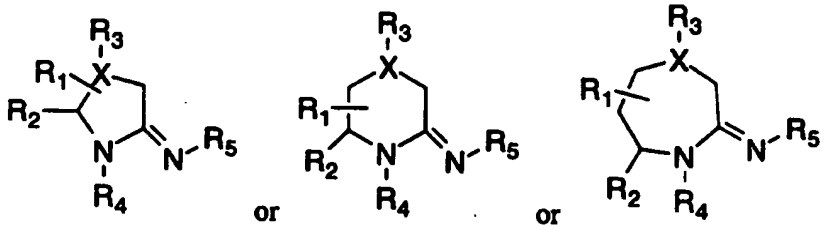
wherein p is 0, 1, or 2 and wherein the second ring may contain up to three hetero atoms selected from N, O or S.

Similarly, compounds of Formula I wherein a member of the group R_1, R_2 and R_3 resides on an atom adjacent to the N on which R_4 resides and forms a ring therewith may be illustrated by:



wherein p is 0, 1, or 2 and wherein the second ring may contain up to three hetero atoms selected from N, O or S

In one preferred aspect the compounds of the invention are of the formulae



wherein

X is selected from CH_2, NH and S,

R_1, R_2 and R_3 are each independently selected from the group consisting of

(a) hydrogen,

(b) linear and branched C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally mono or di- substituted the substituents being independently selected from

(1) carboxy,

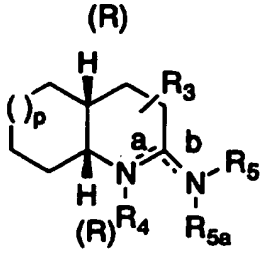
(2) -NHR_7, wherein R_6 and R_7 are each independently hydrogen or C_{1-3}alkyl,

(3) -OR_6,
(4) -$C(O)OR_6$,
(5) -$S(O)_kR_6$, where k is 0, 1 or 2,
(c) hydroxy,
(d) C_{1-6}alkoxy;

R_4 is selected from the group consisting of
(a) hydrogen,
(b) -$C(O)NHR_9$, where R_9 is hydrogen or C_{1-3}alkyl, said C_{1-3}alkyl optionally substituted by
(1) hydroxy,
(2) amino,
(3) carboxy,
(4) -$NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently C_{1-3}alkyl,
(5) -OR_{10},
(6) -$C(O)OR_{10}$,
(7) -$S(O)_mR_{10}$, where m is 0, 1 or 2,
(8) halo selected from F, Cl, Br and I,
(c) -$C(S)NHR_9$;
(d) C_{1-3}alkyl;

R_5 are each independently selected from the group consisting of
(a) hydrogen,
(b) -$C(O)NHR_9$,
(c) -$C(S)NR_8R_9$.
(d) -C_{1-3}alkyl.

In a second preferred aspect the compounds of the invention have cis stereochemistry at the ring junction and are of the formula



wherein p is 1 or 2, and
R_3 and the ring formed by the joining of R_1 and R_2 are optionally mono or di-substituted with substituents selected from the group consisting of

(1) hydroxy,
(2) carboxy,
(3) $-NR_6R_7$, where R_6 and R_7 are each selected from hydrogen, phenyl, cyclohexyl or C_{1-6}alkyl,
(4) $-OR_6$,
(5) $-C(O)OR_6$,
(6) $-S(O)_kR_6$,
(7) halo selected from F, Cl, Br and I,
(8) $-C(=NR_6)-NHR_7$,
(9)-S-$C(=NR_6)-NHR_7$.

Within this second preferred aspect are the compounds wherein
R_3 is selected from

hydrogen, hydroxy or linear and branched C_{1-4}alkyl, said C_{1-4}alkyl,
optionally mono or di- substituted the substituents being independently selected from
(1) carboxy,
(2) $-NHR_7$, wherein R_6 and R_7 are each independently hydrogen or C_{1-3}alkyl,
(3) $-C(O)OR_6$, and
(4) $-S(O)_kR_6$, where k is 1 or 2;

R_4 is selected from the group consisting of
(a) hydrogen,
(b) C_{1-3}alkyl;

R_5 is selected from the group consisting of
(a) hydrogen,
(b) $-C(O)NHR_9$, where R_9 is hydrogen or C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted by
(1) hydroxy,

(2) amino,
(3) carboxy,
(4) -$NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently
C_{1-3}alkyl,
(5) -OR_{10},
(6) -$C(O)OR_{10}$,
(7) -SR_{10}, and
(8) -$S(O)_mR_{10}$, where m is 1 or 2,
(9) halo selected from F, Cl, Br and I,

(c) -$C(S)NR_8R_9$.

(d) C_{1-3}alkyl.

For purposes of this specification alkyl is defined to include linear, branched, and cyclic structures, with C_{1-6}alkyl including methyl, ethyl, propyl, 2-propyl, s- and t-butyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Similarly, C_{1-6}alkoxy is intended to include alkoxy groups of from 1 to 6 carbon atoms of a straight, branched, or cyclic configuration. Examples of lower alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like. Likewise, C_{1-6} alkylthio is intended to include alkylthio groups of from 1 to 6 carbon atoms of a straight, branched or cyclic configuration. Examples of lower alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, etc. By way of illustration, the propylthio group signifies -$SCH_2CH_2CH_3$.

Heteroaryl includes, but is not limited to furan, thiophene, pyrrole, isoxazole, isothiazole, pyrazole, oxazole, thiazole, imidazole, 1,2,3-oxadiazole, 1,2,3-thiadiazole, 1,2,3-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,3,4-triazole, 1,2,5-oxadiazole, 1,2,5-thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine, 1,2,4-triazine, 1,3,5-triazine and 2,4,5-tetrazine.

As outlined in the summary of the invention, the compounds of the instant invention are useful for in the treatment of a number of NOS implicated diseases. The implication of these diseases is well documented in the literature. For example, with regard to psoriasis, see

Ruzicka *et. al.*, J. Invest. Derm., *103*: 397 (1994) or Kolb-Bachofen *et. al.*, Lancet, *344:* 139 (1994) or Bull, et al., *J. Invest. Derm.*, 103:435(1994); with regard to uveitis, see Mandia *et. al.*, Invest Opthalmol., *35*: 3673-89 (1994); with regard to type 1 diabetes, see Eisieik & Leijersfam, Diabetes & Metabolism, *20*: 116-22 (1994) or Kroncke *et. al.*, *BBRC, 175:* 752-8 (1991) or Welsh *et. al.*, *Endocrinol., 129:* 3167-73 (1991); with regard to septic shock, see Petros *et. al.*, Lancet, *338*: 1557-8 (1991),Thiemermann & Vane, Eur. J. Pharmacol., *211*: 172-82 (1992), or Evans *et. al.*, Infec. Imm., *60:* 4133-9 (1992), or Schilling *et. al.*, Intensive Care Med., *19:* 227-231 (1993); with regards to pain, see Moore *et. al.*, Brit. J. Pharmacol., *102*: 198-202 (1991), or Moore *et. al*, Brit. J. Pharmacol., *108*: 296-97 (1992) or Meller *et. al., Europ. J. Pharmacol., 214:* 93-6 (1992) or Lee *et. al., NeuroReport, 3:* 841-4 (1992); with regard to migraine, see Olesen *et. al.*, TIPS, *15:* 149-153 (1994); with regard to rheumatoid arthritis, see Kaurs & Halliwell, FEBS Letters, *350:* 9-12 (1994); with regard to osteoarthritis, see Stadler *et. al., J. Immunol., 147:* 3915-20 (1991); with regard to inflammatory bowel disease, see Miller *et. al.*, Lancet, *34*: 465-66 (1993) or Miller *et. al.*, J. Pharmacol. Exp. Ther., *264*: 11-16 (1993); with regard to asthma, see Hamid *et. al.*, Lancet, *342:* 1510-13 (1993) or Kharitonov, *et. al.*, Lancet, *343:* 133-5 (1994); with regard to Immune complex diseases, see Mulligan *et. al.*, Br. J. Pharmacol., *107*: 1159-62 (1992); with regard to multiple sclerosis, see Koprowski *et. al., PNAS, 90:* 3024-7 (1993); with regard to ischemic brain edema, see Nagafuji *et. al.*, Neurosci., *147*: 159-62 (1992) or Buisson *et. al.*, Br. J. Pharmacol., *106*: 766-67 (1992) or Trifiletti *et. al., Europ. J. Pharmacol., 218:* 197-8 (1992); with regard to toxic shock syndrome, see Zembowicz & Vane, PNAS, *89:* 2051-55 (1992); with regard to heart failure, see Winlaw *et. al.*, Lancet, *344:* 373-4 (1994); with regard to ulcerative colitis, see Boughton-Smith *et. al.*, Lancet *342:* 338-40 (1993); and with regard to atherosclerosis, see White *et. al.*, PNAS, *91:* 1044-8 (1994); with regard to glomerulonephritis, see Mühl *et. al., Br. J. Pharmcol., 112:* 1-8 (1994); with regard to Paget's disease and osteoporosis, see Löwick *et. al., J. Clin. Invest., 93:* 1465-72 (1994); with regard to inflammatory sequelae of viral infections, see

Koprowski *et. al., PNAS, 90:* 3024-7 (1993); with regard to retinitis, see Goureau *et. al., BBRC, 186:* 854-9 (1992); with regard to oxidant induced lung injury, see Berisha *et. al., PNAS, 91:* 744-9 (1994); with regard to eczema, see Ruzica, et al., *J. Invest. Derm.*, 103:395(1994); with regard to acute allograft rejection, see Devlin, J. et al., *Transplantation*, 58:592-595 (1994); and with regard to infection caused by invasive microorganisms which produce NO, see Chen, Y and Rosazza, J.P.N., *Biochem. Biophys. Res. Comm.*, 203:1251-1258(1994).

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic bases and organic bases. Salts derived from inorganic acids include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N_-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethyl-cellulose, methylcellulose, hydroxy-propylmethycellulose, sodium alginate, polyvinyl-pyrrolidone, gum

tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy beans, lecithin,

and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of formula I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

Dosage levels of the order of from about 0.01 mg to about 140 mg/kg of body weight per day are useful in the treatment of the

above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day, preferably 2.5 mg to 1 g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

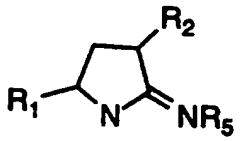
It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

Assay Protocol for NOS activity

NOS activity is measured as the formation of L-[2,3,4,5-^{3}H]Citrulline from L-[2,3,4,5-^{3}H]Arginine. The incubation buffer (100 µL) contained; 100 mM TES, pH 7.5, 5 µM FAD, 5 µM FMN, 10 µM BH_4, 0.5 mM NADPH, 0.5 mM DTT, 0.5 mg/mL BSA, 2 mM CaCl2, 10 µg/mL calmodulin (bovine), 1 µM L-Arg, 0.2 µCi L-[2,3,4,5-^{3}H]Arg, and the inhibitor in aqueous DMSO (max. 5 %). The reaction is initiated by addition of enzyme. Incubations are performed at room temperature for 30 minutes and stopped by the addition of an equal volume of quenching buffer consisting of 200 mM sodium citrate, pH 2.2, 0.02% sodium azide. Reaction products are separated by passing through a cation exchange resin and quantitated as cpm by scintillation counting. Percent inhibition is calculated relative to enzyme incubated without inhibitor according to: % inhibition = 100 x (cpm L-[2,3,4,5-^{3}H]Cit with inhibitor / cpm L-[2,3,4,5-^{3}H]Cit without inhibitor).

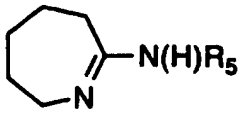
Illustrative of the utility of the compounds of Formula I is the ability of such compounds to inhibit NO synthase as shown in Tables 1-5 and as measured by the assay described above:

TABLE 1



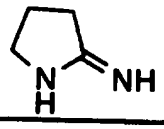
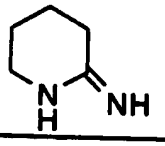
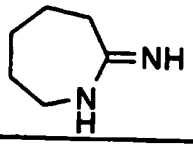
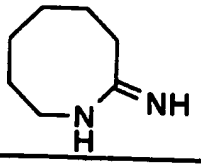
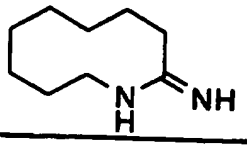
R_1	R_2	R_5	% inhibition (50uM)
H	H	H	90
$-CH_3$	H	H	98
H	$-CH_3$	H	97

TABLE 2



R_5	% inhibition (50uM)
$-CH_3$	3
$-CH_2CH_3$	55
$-CH_2$-phenyl	3
-cyclohexyl	8

TABLE 3

Compound	% inhibition (50uM)
	90
	100
	96
	100
	100

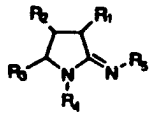


Table 4. Inhibition of Nitric Oxide Synthases by 2-Imino-pyrrolidines

R_1	R_2	R_3	R_4	R_5	IC_{50} (μM)		
					iNOS	ecNOS	ncNOS
H	H	H	H	H	≤ 10	≤ 10	≤ 10
H	H	CO_2H	H	2-thiazolidinyl	≤ 50	NT	NT
H	H	H	H	C_2H_4-Ph-3,4-$(OH)_2$	> 50	> 50	> 50
H	H	CH_3	H	H	≤ 10	≤ 10	≤ 10
CH_3	H	H	H	H	≤ 10	≤ 10	≤ 1
H	H	*cis*-$(CH_2)_3$- [a,b]		H	> 50	≤ 50	≤ 10
H	CH_3	H	H	H	≤ 10	≤ 10	≤ 1
H	CH_3	CH_3	H	H	≤ 1	≤ 1	≤ 1
CH_3	CH_3	H	H	H	≤ 10	≤ 10	≤ 1
CH_3	C_2H_5	H	H	H	≤ 1	> 50	≤ 10
H	CH_3	C_2H_5	H	H	≤ 1	≤ 1	≤ 1
H	C_2H_5	H	H	H	≤ 1	≤ 50	≤ 10
H	n-C_3H_7	H	H	H	≤ 50	> 50	> 50
H	n-C_3H_7	CH_3	H	H	≤ 50	> 50	≤ 50
H	n-C_3H_7	C_2H_5	H	H	≤ 50	> 50	≤ 50

[a] Substituents that form a ring between adjacent atoms should be read from left to right. Thus, when R_3-R_4 = "-$(CH_2)_3$-" the ring is intended to begin at the carbon containing R_3 and ending at the carbon containing R_4. [b] The terms *cis* and *trans* designate the relative configuration of the ring junction.

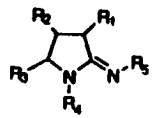


Table 4. Inhibition of Nitric Oxide Synthases by 2-Imino-pyrrolidines

R_1	R_2	R_3	R_4	R_5	IC_{50} (μM)		
					iNOS	ecNOS	ncNOS
H	H	$(CH_3)_2$	H	H	≤ 10	≤ 50	≤ 10
H	i-C_3H_7	H	H	H	≤ 10	> 50	≤ 50
H	H	C_2H_5	H	H	≤ 50	≤ 10	≤ 10
H	CH_3	CH_3	H	H	≤ 1	≤ 1	≤ 1
H	CH_3	CH_3	H	H	≤ 1	≤ 1	≤ 1
H	CH3	n-C3H7	H	H	≤ 10	≤ 50	≤ 10
H	C_2H_5	CH_3	H	H	≤ 1	≤ 10	≤ 1
H	H	(S)-CH_2OAc	H	H	≤ 50	> 50	≤ 10
H	H	(S)-CH_2OH	H	H	≤ 10	> 50	≤ 50
H	H	(R)-CH_2OAc	H	H	> 50	> 50	> 50
H	H	(R)-CH_2OH	H	H	≤ 50	≤ 50	≤ 50
- $(CH_2)_3$ -		H	H	H	≤ 10	≤ 10	≤ 1
- $(CH_2)_4$ -		H	H	H	≤ 10	≤ 50	≤ 1
H	H	C(=O)NH$(CH_2)_2$C(=NH)NH_2	H	H	≤ 10	> 50	< 10
SH	H	H	H	H	≤ 50	≤ 50	≤ 1

[a] Substituents that form a ring between adjacent atoms should be read from left to right. Thus, when R_3-R_4 = "-$(CH_2)_3$-" the ring is intended to begin at the carbon containing R_3 and ending at the carbon containing R_4. [b] The terms *cis* and *trans* designate the relative configuration of the ring junction.

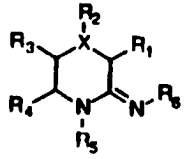


Table 5. Inhibition of Nitric Oxide Synthases by 2-Imino-piperidines

X	R_1	R_2	R_3	R_4	R_5	R_6	IC_{50} (μM) iNOS	ecNOS	ncNOS
CH	H	H	*trans* - $(CH_2)_4$ -	c	H	H	≤ 1	≤ 10	≤ 1
CH	H	H	*cis* - $(CH_2)_4$ -		H	H	≤ 1	≤ 50	≤ 1
N	H	H	*cis* - $(CH_2)_4$ -		H	H	≤ 10	> 50	> 50
CH	H	H	CF_3	H	H	H	≤ 10	> 50	> 50
CH	H	CH_3	cyclo-C_6H_{12}	H	H	H	> 50	> 50	> 50
CH	C_2H_5	CH_3	H	H	H	H	≤ 50	≤ 50	≤ 10
CH	CH_3		- $(CH_2)_3$ -	H	H	H	≤ 10	> 50	≤ 10
CH	H	CH_3	NHAc	H	H	H	≤ 50	> 50	> 50
CH	H	CH_3	CO_2CH_3	H	H	H	≤ 10	> 50	≤ 50
CH	H	H	O-n-C_3H_7	H	H	H	≤ 1	≤ 10	≤ 10
CH	n-C_3H_7	CH_3	H	H	H	H	≤ 50	> 50	≤ 50
CH	H	CH_3	CH_2NHAc	H	H	H	≤ 50	> 50	≤ 50
CH	H	CH_3	Δ^5, -$(CH{=}CH)_2$-		H	H	≤ 1	≤ 50	≤ 1
N	H	CO_2-t-C_4H_9	H	H	H	H	≤ 50	> 50	> 50
N	H	H	H	H	H	H	≤ 50	> 50	≤ 50
CH	H	CH_3	CO_2H	H	H	H	≤ 10	≤ 50	≤ 10
CH	H	(S)-CH_3	(S)-OH	H	H	H	≤ 1	≤ 10	≤ 1
CH	H	(S)-CH_3	(S)-OCH_3	H	H	H	≤ 1	≤ 1	≤ 1

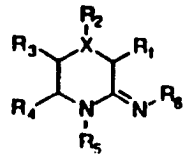


Table 5. Inhibition of Nitric Oxide Synthases by 2-Imino-piperidines

X	R_1	R_2	R_3	R_4	R_5	R_6	IC_{50} (μM) iNOS	ecNOS	ncNOS
CH	H	CF_3	H	H	H	H	≤ 10	≤ 10	≤ 10
CH	H	H	CH_3, *trans*-(CH(OH)$(CH_2)_3$)-		H	H	> 50	> 50	> 50
CH	H	OCH_3	H	H	H	H	≤ 1	≤ 10	≤ 1
CH	H	CH_3	C_2H_5	H	H	H	≤ 1	≤ 10	≤ 1
CH	H	(S)-CH_3	(R)-CH_3	H	H	H	≤ 1	≤ 10	≤ 1
CH	(3S, 4R)-(O$C(CH_3)_2$O)-		(R)-OAc	H	H	H	> 50	> 50	> 50
CH	H	H	H	H	CH3	H	≤ 50	> 50	> 50
CH	(S)-OAc	(R)-OAc	(R)-OAc	H	H	H	> 50	> 50	> 50
CH	H	H	H	H	C(=O)NHCH_2Ph	H	> 50	> 50	> 50
N	H	CH_3	H	H	H	H	≤ 10	≤ 10	≤ 10
O	H	-	*cis*-$(CH_2)_5$-		H	H	≤ 50	> 50	≤ 50
CH	H	H	*cis*-(($CH_2)_2$C(O$(CH_2)_2$O)CH_2)-		H	H	> 50	> 50	> 50
CH	H	H	-(CH_2C(O$(CH_2)_2$O)$(CH_2)_2$)-		H	H	≤ 50	> 50	> 50
CH	H	CH_3	n-C_5H_{11}	H	H	H	≤ 10	> 50	≤ 50
CH	CH_3	H	*cis*-(CH_2O$(CH_2)_2$)-		H	H	> 50	> 50	> 50
CH	H	H	-(CHC(=O)$(CH_2)_2$-		H	H	≤ 50	> 50	≤ 50
N	H	C(=O)CH_3	Δ^5, -(CH=CH)$_2$-		H	H	> 50	> 50	≤ 50

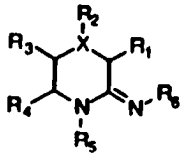


Table 5. Inhibition of Nitric Oxide Synthases by 2-Imino-piperidines

X	R_1	R_2	R_3	R_4	R_5	R_6	IC_{50} (μM) iNOS	ecNOS	ncNOS
CH	H	H	*cis*-$((CH_2)_2C(=O)CH_2)$-		H	H	≤ 1	≤ 50	≤ 1
CH	H	H	-$(CF(CH_3)(CH_2)_3)$-		H	H	≤ 50	> 50	> 50
N	H	$C(=O)OCH_2Ph$	Δ^5, -$(CH=CH)_2$-		H	H	> 50	> 50	> 50
N	H	CH_3	Δ^5, -$(CH=CH)_2$-		H	H	≤ 50	> 50	≤ 10
N	H	H	Δ^5, -$(CH=CH)_2$-		H	H	≤ 50	≤ 50	≤ 10
CH	H	H	*trans*-$((CH_2)_2CH(OAc)CH_2)$-		H	H	≤ 50	> 50	≤ 10
CH	H	H	H	H	CH_2Ph-4-OCH_3	C(=O)NHPh	> 50	> 50	> 50
CH	H	H	H	H	CH_2Ph	C(=O)NHPh	> 50	> 50	> 50
CH	H	H	H	H	H	C(=O)NHPh	≤ 50	> 50	≤ 50
CH	H	H	*cis*-$(CH(OAc)(CH_2)_3$-		H	H	> 50	> 50	> 50
CH	H	(R)-CH_3	(S)-CH_3	H	H	H	≤ 1	≤ 10	≤ 1
CH	H	(S)-CH_3	(S)-CH_3	H	H	H	≤ 1	< 10	< 1
CH	H	(R)-CH_3	(R)-CH_3	H	H	H	≤ 1	< 10	< 1
CH	H	*cis*-CH_3	*cis*-$(CH_2)_3$-		H	H	≤ 1	≤ 1	≤ 1
N	H	Ac	*trans*-$(CH_2)_4$-		H	H	> 50	> 50	> 50
CH	H	H	*cis*-$(CH(OH)(CH_2)_3$-		H	H	> 50	> 50	> 50

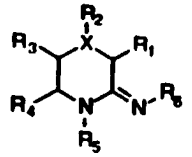


Table 5. Inhibition of Nitric Oxide Synthases by 2-Imino-piperidines

X	R_1	R_2	R_3	R_4	R_5	R_6	IC_{50} (μM) iNOS	ecNOS	ncNOS
CH	H	H	*trans*-$(CH_2)_2CH(OH)CH_2$-		H	H	> 50	> 50	> 50
CH	H	CH3	Δ^5, -$CH_2O(CH_2)_2$-		H	H	≤ 50	> 50	> 50
CH	H	H	*cis*- $CH_2CH(OAc)(CH_2)_2$-		H	H	> 50	> 50	>50
CH	H	H	*cis*--$CH_2CH(OH)(CH_2)_2$-		H	H	> 50	> 50	> 50
CH	H	H	-$(CH_2)_2CH(OAc)CH_2$-		H	H	≤ 50	> 50	≤ 50
CH	H	(4S)-CH_3	*cis*-(5S,6R)-$(CH_2)_4$-		H	H	> 50	> 50	≤ 1
CH	H	(4R)-CH_3	*cis*-(5R,6S)-$(CH_2)_4$-		H	H	≤ 1	≤ 1	≤ 1
CH	H	(4S)-CH_3	*cis*-(5S,6R)-$(CH_2)_3$-		H	H	≤ 1	≤ 1	≤ 1
CH	H	(4R)-CH_3	*cis*-(5R,6S)-$(CH_2)_3$-		H	H	≤ 1	≤ 1	≤ 1
CH	H	CH_3	*cis*-$CH_2O(CH_2)_2$-		H	H	> 50	> 50	>50
N	H	CH_3	(=O)	i-C_4H_9	H	H	> 50	> 50	> 50
CH	H	(R)-CH_3	(S)-OH	H	H	H	≤ 50	≤ 50	≤ 10
CH	H	(R)-CH_3	(S)-OCH_3	H	H	H	≤ 10	≤ 50	≤ 10
N	H	CH_3	*trans*-$(CH_2)_4$-		H	H	> 50	> 50	≤ 10
S	H	-	H	n-C_3H_7	H	H	≤ 1	≤ 1	≤ 50
CH	H	H	*cis*-$CH(OCH_3)(CH_2)_2$-		H	H	> 50		
CH	H	H	*cis*-$CH(OH)(CH_2)_2$-		H	H	> 50		
N	H	CH3	H	CH3	H	H			

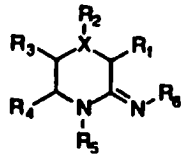


Table 5. Inhibition of Nitric Oxide Synthases by 2-Imino-piperidines

X	R_1	R_2	R_3	R_4	R_5	R_6	IC_{50} (μM) iNOS	ecNOS	ncNOS
CH	NH2	H	H	H	H	H	<10	<10	<10
CH	H	H	*cis*-C(=O)$(CH_2)_2$-		H	H			
CH	H	H	*cis*-CH(OAc)$(CH_2)_2$-		H	H			
S	H		H	C_2H_5	H	H	<1	<1	<1
S	H		H	n-C_4H_9	H	H	<1	<10	<1
S	H		H	CH_3	H	H	<1	<1	<1

[a] The designation "Δ" followed by a numeral indicates the presence of a double bond from that carbon to the next adjacent carbon (eg., "Δ^5" indicates a carbon-carbon double from C_5 to C_6. [b] Substituents that form a ring between adjacent atoms should be read from left to right. Thus, when R_3-R_4 = "-$(CH{=}CH)_2$-" the ring is intended to begin at the carbon containing R_3 and ending at the carbon containing R_4. [c] The terms *cis* and *trans* designate the relative configuration of the ring junction.

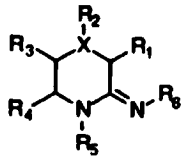


Table 6. Inhibition of Nitric Oxide Synthases by 2-Imino-piperidines

X	R_1	R_2	R_3	R_4	R_5	R_6	IC_{50} (μM) iNOS	ecNOS	ncNOS
CH	H	H	H	H	H	H	≤ 1	≤ 1	≤ 1
CH	H	H	Δ^5, -(CH=CH)$_2$- [a,b]		H	H	≤ 50	> 50	≤ 10
CH	CH_3	H	H	H	H	H	≤ 10	≤ 10	≤ 1
CH	H	H	CH_3	H	H	H	≤ 1	≤ 10	≤ 10
CH	H	CH_3	H	H	H	H	≤ 1	≤ 1	≤ 1
CH	H	n-C_3H_7	H	H	H	H	≤ 10	> 50	> 50
CH	CH_3	H	CH_3	H	H	H	≤ 50	≤ 50	≤ 1
CH	H	H	$(CH_3)_2$	H	H	H	≤ 10	≤ 50	≤ 10
CH	H	H	(R)-CH_3	H	H	H	≤ 1	≤ 10	≤ 10
CH	H	H	(S)-CH_3	H	H	H	≤ 10	≤ 10	≤ 10
CH	H	(R)-CH_3	H	H	H	H	≤ 1	≤ 1	≤ 1

[a] The designation "Δ" followed by a numeral indicates the presence of a double bond from that carbon to the next adjacent carbon (eg., "Δ^5" indicates a carbon-carbon double from C_5 to C_6. [b] Substituents that form a ring between adjacent atoms should be read from left to right. Thus, when R_3-R_4 = "-(CH=CH)$_2$-" the ring is intended to begin at the carbon containing R_3 and ending at the carbon containing R_4. [c] The terms *cis* and *trans* designate the relative configuration of the ring junction.

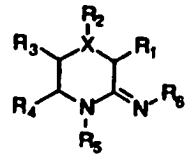


Table 6. Inhibition of Nitric Oxide Synthases by 2-Imino-piperidines

X	R_1	R_2	R_3	R_4	R_5	R_6	IC_{50} (μM) iNOS	ecNOS	ncNOS
CH	H	(S)-CH_3	H	H	H	H	≤ 1	≤ 1	≤ 1
CH	H	CH_3	CH_3	H	H	H	≤ 1	≤ 1	≤ 1
C	Δ^3, -$(CH=CH)_2$-		H	H	H	H	≤ 10	≤ 50	≤ 10
N	H	H	- $(CH_2)_4$ -		H	H	≤ 10	> 50	≤ 50
CH	H	CH_3	H	CH_3	H	H	≤ 1	≤ 1	≤ 1
S	H	-	H	H	H	H	≤ 1	≤ 10	≤ 1

[a] The designation "Δ" followed by a numeral indicates the presence of a double bond from that carbon to the next adjacent carbon (eg., "Δ^5" indicates a carbon-carbon double from C_5 to C_6. [b] Substituents that form a ring between adjacent atoms should be read from left to right. Thus, when R_3-R_4 = "-$(CH=CH)_2$-" the ring is intended to begin at the carbon containing R_3 and ending at the carbon containing R_4. [c] The terms *cis* and *trans* designate the relative configuration of the ring junction.

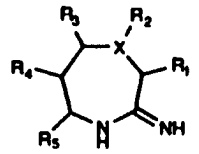


Table 7. Inhibition of Nitric Oxide Synthases by Imino Azepines and 1,4-Heteroazepines

						IC_{50} (μM)		
X	R_1	R_2	R_3	R_4	R_5	iNOS	ecNOS	ncNOS
CH	H	H	H	H	H	≤ 10	≤ 10	≤ 1
CH	H	H	H	H	n-C_3H_7	≤ 1	≤ 10	≤ 1
CH	NH_2	H	H	H	H			
N	H	H	H	H	H	≤ 1	≤ 10	≤ 1
N	H	CH_3	H	H	H	> 50	> 50	> 50
N	H	H	CH_3	H	H	≤ 10	> 50	> 50
N	H	C(=O)O-t-C_4H_9	H	H	H	> 50	> 50	> 50
N	H	H	H	CH_3	H			
N	H	H	H	H	CH_3			
N	H	H	H	H	n-C_3H_7	> 50		
N	H	H	H	*cis*-$(CH_2)_4$- [a,b]		≤ 10	> 50	≤ 10
S	H	H	H	H	H	≤ 10	≤ 50	≤ 10
O	H	H	H	H	H	≤ 1	≤ 1	≤ 1
O	H	H	H	H	n-C_3H_7			

[a] Substituents that form a ring between adjacent atoms should be read from left to right. Thus, when R_4-R_5 = "-$(CH_2)_4$-" the ring is intended to begin at the carbon containing R_4 and ending at the carbon containing R_5. [b] The terms *cis* and *trans* designate the relative configuration of the ring junction.

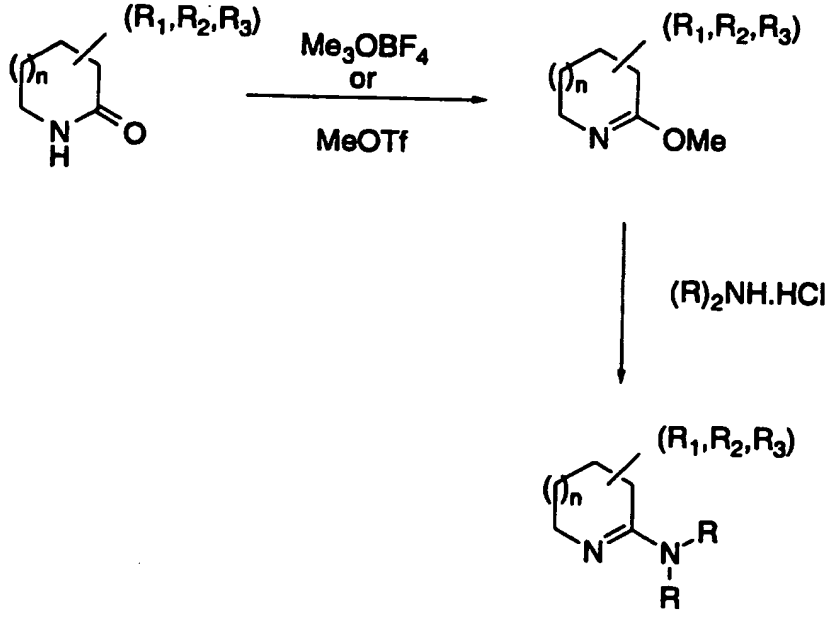
TABLE 8

Stereochemical Preferences for NOS Inhibition

Example No.	iNOS IC_{50} (uM)	ecNNOS IC_{50} (uM)	ncNOS IC_{50} (uM)
87	0.015	0.05	0.02
88	0.022	0.1	0.009
89	0.24	7.3	1.2
90	1.63	9.9	5.0
91	0.62	8.3	0.58
92	0.14	1.9	0.25
93	0.42	3.4	0.42
94	0.1	2.2	0.12
95	0.038	0.65	0.12
96	0.047	2.3	0.75
97	4.5	> 20	2.2
98	13.3	> 20	8.0
103	0.528	5.5	5.5
102	0.186	12.5	0.246
104	0.133	0.87	0.036
104	0.009	0.36	0.021
105	> 2.5	> 2.5	0.61
105	0.02	0.83	0.053

Several methods for preparing the compounds of this invention are illustrated in the following schemes and examples. Some of the compounds are known in the literature but none are reported to be inhibitors of NO Synthase. In one method outlined in scheme 1 and illustrated in Example 2, the compounds are prepared by reacting a cyclic iminoether with an appropriate amine or its salt such as a hydrochloride, hydrobromide, sulfate, alkyl sulfonate, acetate etc at a temperature between 0-100 °C. The required intermediate iminoether substrates can be prepared by O-alkylation of the corresponding lactam by reagents such as methyl trifluoromethanesulfonate, trimethyloxonium fluoborate, methyl sulfate etc. Other methods for preparation of iminoether known in the art of organic synthesis may also be employed. Many of the lactam starting materials are commercially available or they can be obtained by literature procedures. One useful method for the preparation of substituted lactams is illustrated in example 1.

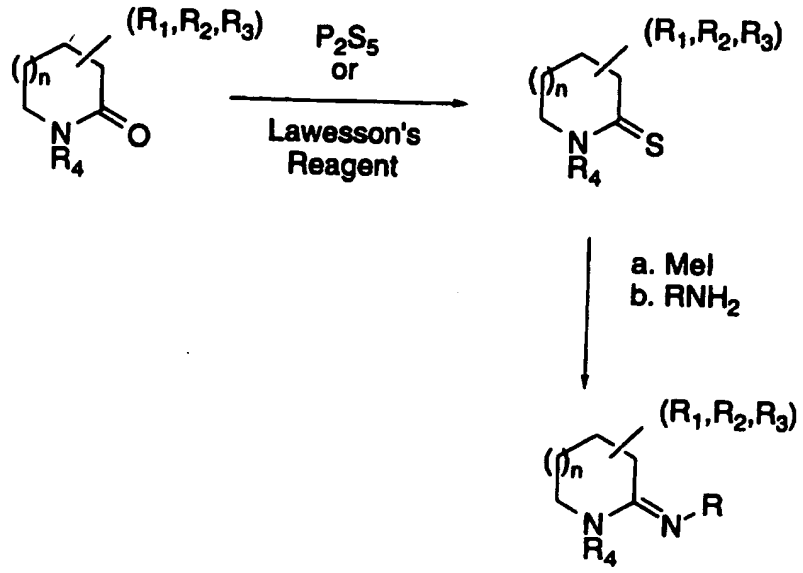
SCHEME 1



Another method for preparing compounds of this invention is shown in scheme 2. In this method a thiolactam is first reacted with an

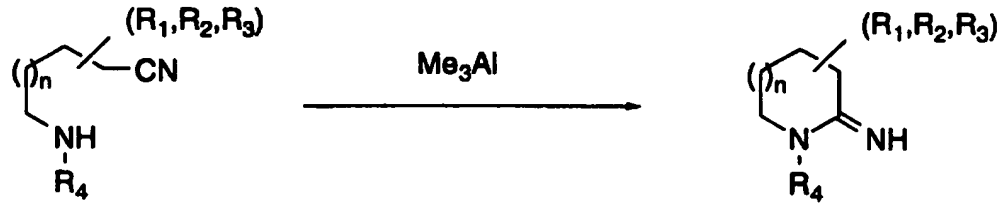
alkylating agent such as methyl iodide or methyl sulfate and the resulting iminothioether salt is reacted with an amine to furnish the desired amidines. The thiolactam substrates for this process are known in the literature or they can be prepared from the corresponding lactam by treatment with reagents such as P_2S_5 or Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide) as illustrated in example 3.

SCHEME 2



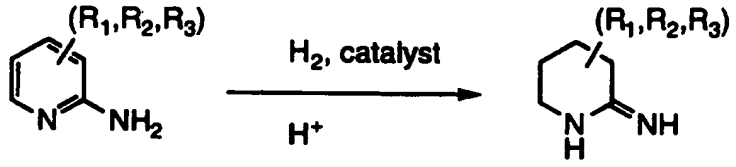
Alternatively, the cyclic amidine compounds may also be synthesized from acyclic precursors as described by Garigipati (*Tet. Lett.* 31, 1969-1972 (1990)). In this method (Scheme 3) an amino nitrile is converted to an aluminum amide by reaction with an alkylaluminum reagent such as trimethylaluminum and in situ cyclization of this intermediate furnishes the desired amidines.

SCHEME 3



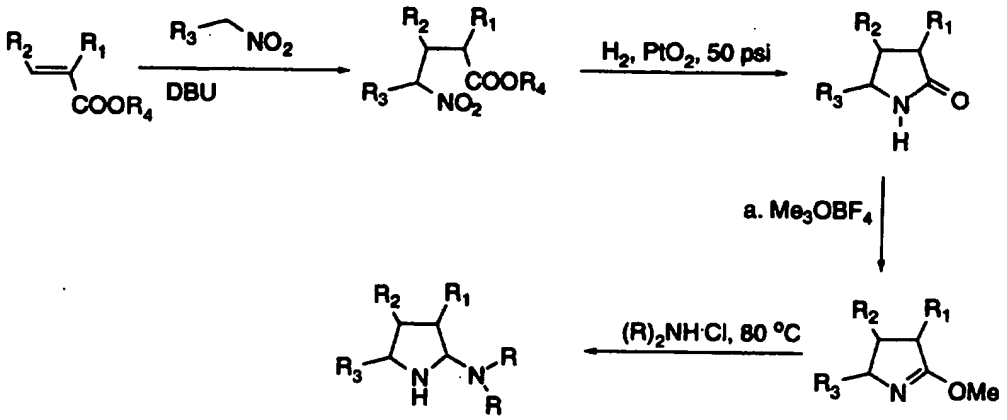
Alternatively, the cyclic amidine compounds may also be synthesized from substituted or unsubstituted 2-aminopyridines by the method of Freifelder (M. Freifelder, R. W. Mattoon, Y. H. Ng, *J. Org. Chem.*. *29*, 3730-3732 (1964)) employing catalytic hydrogenation under acidic conditions (Scheme 4). The addition of acid during the hydrogenation is important (T. B. Grave, *J. Am. Chem. Soc. 46*, 1460-1470 (1924))

SCHEME 4



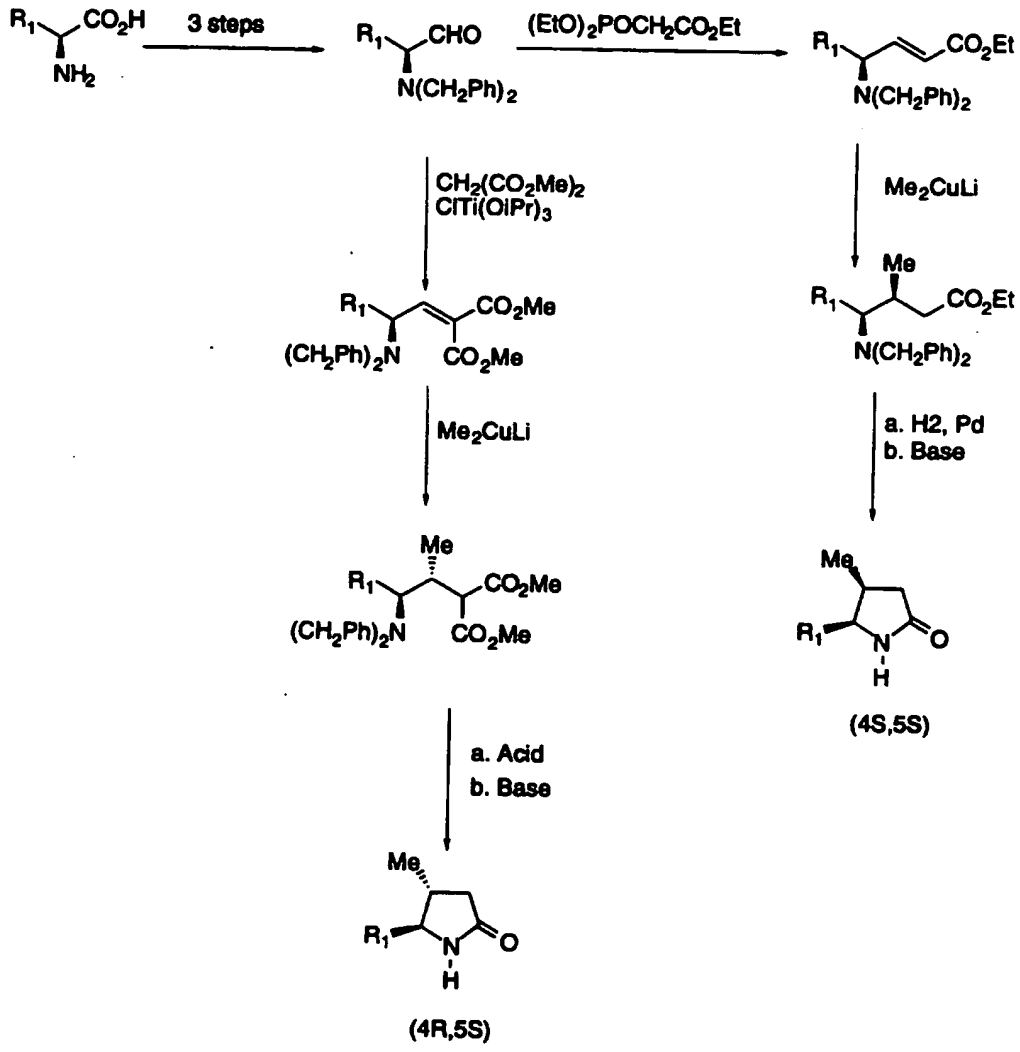
Cyclic amidines may also be prepared from acyclic precursors as shown in scheme 5 and demonstrated in example 6. Thus, a Michael addition of a nitroalkane to an acrylate ester by the method of Bunce and Drumright (*Org. Prod. Prep. Int.* 19, 471-475 (1987)) leads to an ester of 4-nitrobutyric acid. Reduction of the nitro group and cyclization gives a lactam which is converted to an amidine by the procedures described in scheme 1 or 2.

SCHEME 5



Many cyclic amidines claimed in this specification can have stereoisomers and such individual stereoisomers may be prepared from chiral lactams. Numerous methods for the synthesis of stereochemically pure lactams have been described in literature. One such method using amino acids as starting materials is described by Reetz and Rohrig (*Angew. Chem. Int. Ed. Engl.* 28, 1706-1709 (1989)) and is shown in scheme 6. The key feature of this procedure is the stereospecific addition of organometallic reagents to an unsaturated ester and the reversal of the stereoselectivity with an unsaturated malonate, thus allowing synthesis of two diastereomers from the same aldehyde intermediate.

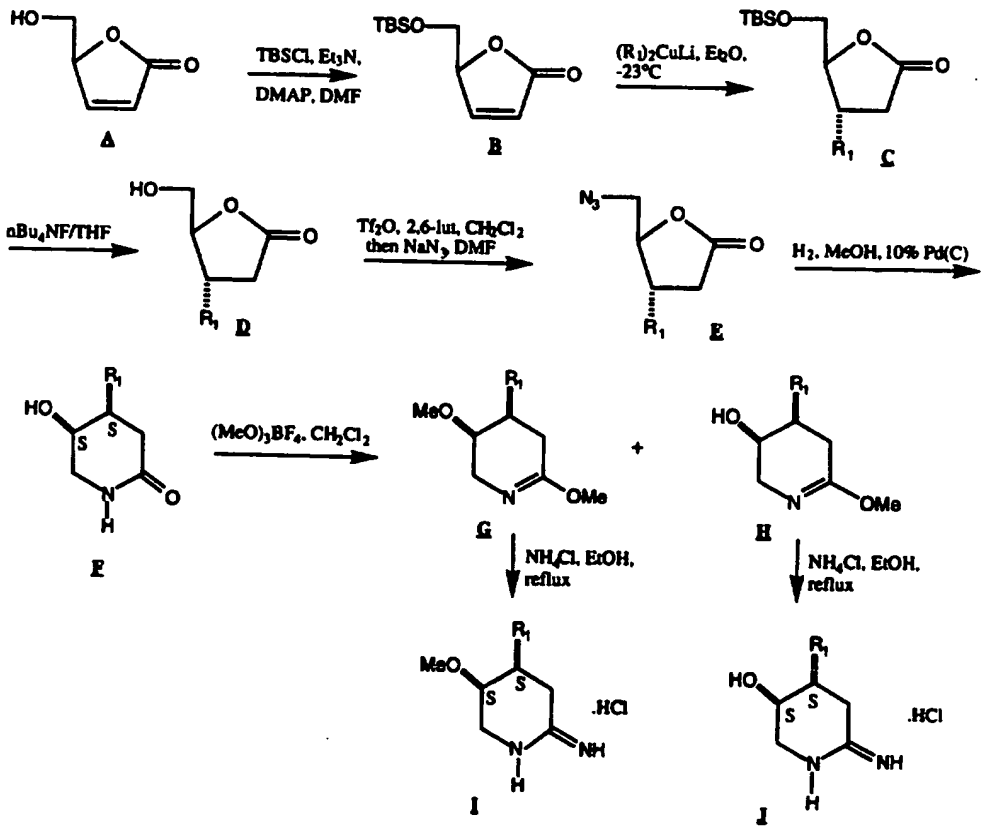
Scheme 6



Synthetic methodology also exists for the preparation of chirally substituted 2-imino-piperidines. As shown in Scheme 7, addition of organocuprates to the O-*tert*-butyldimethylsilyl-protected (S)-(-)-5(hydroxymethyl)-2(5H)-furanone **B** derived from **A** (available from Aldrich Chemical Co., Milwaukee, WI) will yield stereoisomer **C** (S.

Hanessian and P. J. Murray, *Tetrahedron* , *43*, 5055-5072 (1987)). Deprotection of C yields the free alcohol D which is converted to lactam F by described methodology (C. Herdeis and D. Waibel, *Arch. Pharm. (Weinheim)* **1991**, *324*, 269-274). Treatment with Meerwien's salt followed by reaction with ammonium chloride in refluxing ethanol yields chiral 2-imino-piperidines I and J. Other substituents and substitution patterns are available by analogous chemical manipulations from described intermediates (S. Hanessian, *Aldrichimica Acta 22*, 3-15 (1989)).

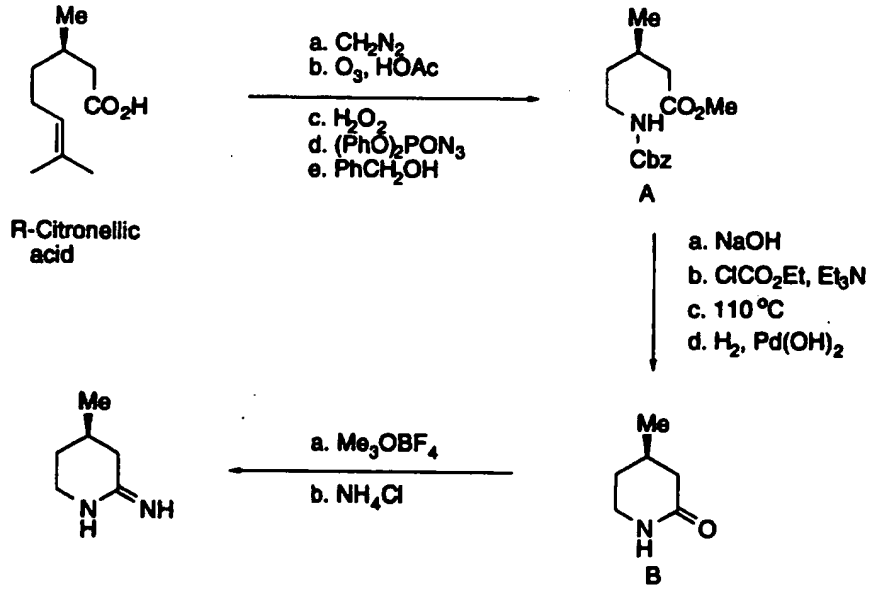
SCHEME 7



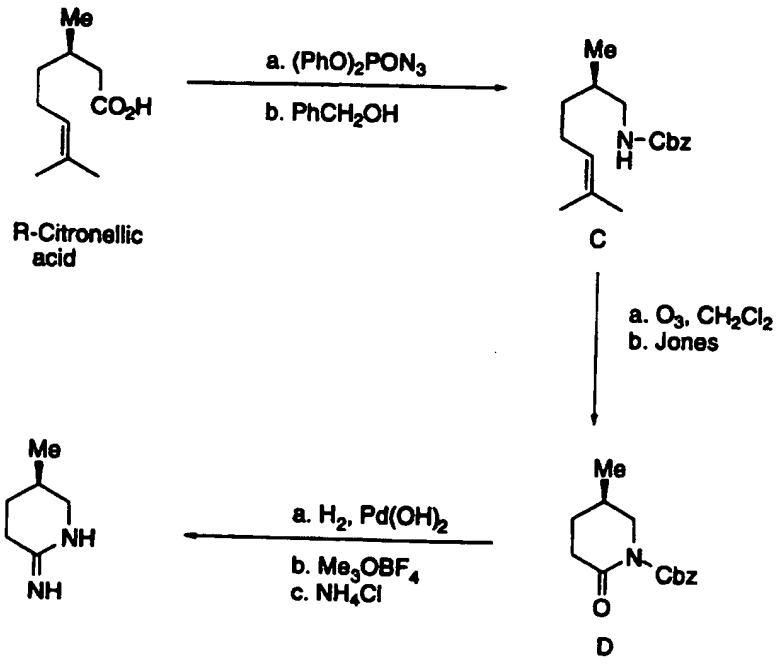
Another method for the synthesis of chiral amidines is shown scheme 8. This synthesis utilizes commercially available individual enantiomers of citronellic acid that allow preparation of chiral

2-iminopiperidines. Treatment of methyl citronellate with ozone and further oxidation of the intermediate gives an acid which was used in a Curtius reaction to furnish **A** upon reaction with benzyl alcohol. Hydrolysis, cyclization and removal of the Cbz group of **A** leads to a chiral lactam (**B**) and reaction of **B** with trimethyloxonium fluoroborate followed by NH_4Cl as detailed in scheme 1 furnishes a cyclic amidine. Citronellic acid is also a useful starting material for chiral 5-methyl-2-iminopiperidines as shown in scheme 9. In this case citronellic acid is first subjected to the Curtius reaction to give a protected amine (**C**). Cleavage of the double bond of **C** by ozone and further oxidation directly leads to **D** and this lactam is converted to an enantiomerically pure amidine in 3 steps.

Scheme 8

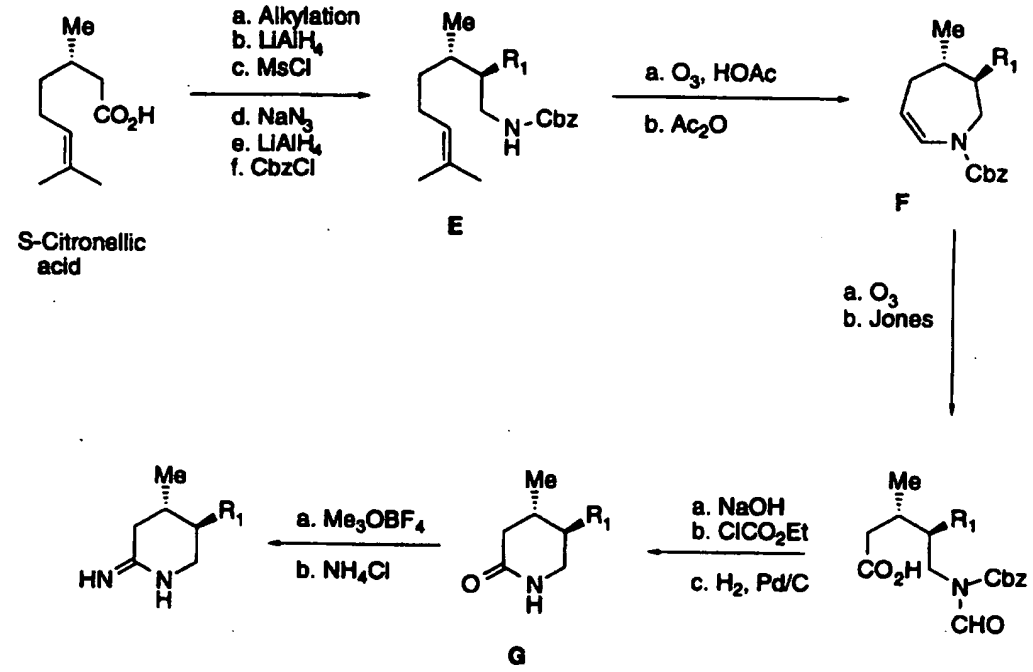


Scheme 9



Citronellic acid can also be used in the synthesis of chiral 4,5-disubstituted 2-iminopiperidines as shown in shown in scheme 10. This method relies on stereoselective alkylation using the oxazolidone chiral auxiliary developed by Evans (*J. Amer. Chem. Soc.* 104, 1737-1739 (1982)) and the product is then converted to **E**. Ozonolysis of the double bond of **E** and cyclization of the resulting aldehyde gives **F**. Treatment of **F** with ozone followed by further oxidation gives an amino acid which is cyclized to a chiral lactam (**G**). Usual transformation of **G** furnishes cyclic amidine.

Scheme 10

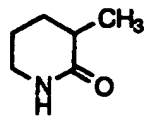


The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

All operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm. Hg) with a bath temperature of up to 60°C; the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only; melting points are uncorrected and 'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations; the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry,

nuclear magnetic resonance (NMR) spectrometry or microanalytical data; yields are given for illustration only; when given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 400 MHz or 500 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal; chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

EXAMPLE 1



3-Methyl-2-piperidone

Step A: 1-(1,2-diphenyl-2-hydroxy)ethyl-3-methylpiperidine.

A mixture of 1.96 g (10 mmoles) of commercially available trans-stilbene oxide and 990 mg (10 mmoles) of 3-methyl piperidine was heated one day in refluxing ethanol. The solvent was then removed in vacuo to give the desired amino alcohol in quantitative yield.

Step B: 1-(1,2-diphenyl-2-hydroxy)ethyl-3-methyl-2-piperidone & 1-(1,2-diphenyl-2-hydroxy)ethyl-5-methyl-2-piperidone

A mixture of the crude amino alcohol(10 mmoles) from step A, 6.39 g (20 mmoles) of mercuric acetate and 7.5 g (20 mmoles) of ethylene diamine tetraacetic acid disodium salt in 80 mL of 1% acetic acid in water was heated to reflux 1.5 hrs. After cooling the reaction mixture, methylene chloride was added and the mixture was swirled around to dissolve all organic matter. The organic and aqueous layers were decanted from the shiny metallic mercury by-product. The aqueous layer was separated and extracted further with methylene chloride. The combined organic layers were washed with water and saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, solvent was removed to give a brown crude product, which was puridfied on silica gel using 1:3 ethyl acetate and hexane mixture to give 639 mg of 1-(1,2-diphenyl-2-hydroxy)ethyl-3-methyl-2-piperidone and 1.5 g of 1-(1,2-diphenyl-2-hydroxy)ethyl-5-methyl-2-piperidone.

Step C: 1-(1,2-diphenyl-2-oxo)ethyl-3-methyl-2-piperidone.

0.7 mL of 8N Jones reagent was added dropwise to an ice-cooled solution of 620 mg (2 mmoles) of 1-(1,2-diphenyl-2-hydroxy)ethyl-3-methyl-2-piperidone in 10 mL of acetone. The reaction mixture was then stirred one hour. 1 mL of isopropyl alcohol was added and the mixture was stirred 10 minutes. The solvent was then removed in vacuo. The residue was stirred with water and ethyl acetate until all solids dissolved. The aqueous phase was separated and extracted with ethyl acetate. The combined ethyl acetate phases were washed with water and saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvent was removed in vacuo to afford the desired lactam ketone as foam in quantitative yield.

Step D: 3-Methyl-2-piperidone

A mixture of 550 mg (1.8 mmoles) of 1-(1,2-diphenyl-2-oxo)ethyl-3-methyl-2-piperidone and 715 mg (11 mmoles) of zinc dust in 8 mL of glacial acetic acid was heated to reflux for 1 day. The mixture was cooled and filtered and the solids washed with ethyl acetate. The filtrate was concentrated to ~5 mL. 25 mL of toluene was added and the solvents were removed in vacuo. The residue was dissolved in ethyl acetate and made basic with cautious addition of concentrated ammonium hydroxide. The initially formed precipitate dissolved upon further addition. After stirring 10 minutes, anhydrous magnesium sulfate was added in excess. After 20 minutes, the solids were filtered and washed with ethyl acetate. The filtrate was concentrated to give a residue which was purified on silica gel using 1:1 mixture of ethyl acetate and hexane first and then using 10% methanol in ethyl acetate to give 148 mg of 3-methyl-2-piperidone as fluffy solid.

^{1}H NMR($CDCl_3$): 3.3 (m, CH_2N); 2.48 (m, $CH_2C{=}O$); 1.45-2.0 (m, CH_2's); 1.24 (d, CH_3); 5.95 (b,NH)

Following the above procedures, the following lactams were synthesized:

5-Methyl-2-piperidone:

^{1}H NMR($CDCl_3$): 3.3 & 2.92 (m, CH_2N); 2.35 (m, $CH_2C=O$); 1.4-2.0 (m, CH_2's); 1.0 (d, CH_3); 6.1 (b,NH)

4-Methyl-2-piperidone:

^{1}H NMR($CDCl_3$): 3.35 (m, CH_2N); 2.48 & 2.8 (m, $CH_2C=O$); 1.35-2.04 (m, CH_2's); 1.04 (d, CH_3); 6.05 (b,NH)

4-Propyl-2-piperidone:

^{1}H NMR($CDCl_3$): 3.32 (m, CH_2N); 2.5 & 1.98 (m, $CH_2C=O$); 1.25-1.95 (m, CH_2's); 0.90 (t, CH_3); 6.1 (b,NH)

5,5-Dimethyl-2-piperidone:

^{1}H NMR($CDCl_3$): 3.01 (s, CH_2N); 2.38 (t, $CH_2C=O$); 1.60 (t, CH_2); 1.04 (s, CH_3's); 6.1(b,NH)

3,5-Dimethyl-2-piperidone:

^{1}H NMR($CDCl_3$): 3.3 & 2.9 (m, CH_2N); 2.52 (m, CHC=O); 1.56-2.1 (m, CH_2's); 1.0 & 1.28 (d, CH_3's); 5.95(b,NH)

4-Benzyl-2-piperidone:

^{1}H NMR($CDCl_3$): 3.3 (m, CH_2N); 2.62 (m, $CH_2C=O$); 1.35-2.48 (m, CH_2's); 7.1-7.3 (m, Aromatic); 6.05 (b,NH)

4-Ethoxycarbonyl-2-piperidone:

^{1}H NMR($CDCl_3$): 4.16 (q; CH_2O); 3.35 (m, CH_2N); 2.60 (d, $CH_2C=O$);2.80 (CHCOOEt); 1.82-2.16 (m, CH_2's); 1.24 (t, CH_3); 6.58 (b,NH)

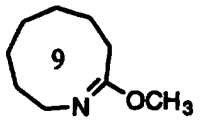
1,2,3,4-Tetrahydro-1-quinolone:

^{1}H NMR($CDCl_3$): 3.6 (t, CH_2N);3.0 (t, CH_2); 7.2-8.05 (m, Aromatic); 6.6 (b,NH)

4-Ethoxycarbonyl-2-piperizinone:

^{1}H NMR($CDCl_3$): 4.26 (q, CH_2O);4.12 (s, $NCH_2C{=}O$); 3.38 & 3.66 (b, CH_2's); 1.26 (t, CH_3); 6.66 (b, NH)

EXAMPLE 2



1-Aza-2-methoxy-1-cyclononene

Trimethyloxonium tetrafluoroborate (750 mg; 5 mmol) was added in one portion to 2-azacyclononanone (700 mg; 5 mM) in 10 mL of anhydrous methylene chloride. The resulting mixture was stirred overnight at room temperature. The next morning10% Sodium bicarbonate solution was cautiously added to neutralize fluoroboric acid and the mixture was then diluted with 20 mL of ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with 10% sodium bicarbonate solution and with brine. After drying over anhydrous magnesium sulfate, the organic layer was concentrated to remove the solvents. The residue was taken up in hexane and filtered through a small bed of wet silica gel in hexane. The filtrate was concentrated to give 320 mg of the desired 1-aza-2-methoxy-1-cyclononene.

^{1}H NMR: 3.52 (s, OCH_3), 3.36 (m, $CH_2N{=}$), 2.24 (m, $N{=}C{-}CH_2$); 1.3-1.7(m).

The following iminoethers were synthesized according to the above general procedure. In the case of low molecular weight imino ethers such as 1-aza-2-methoxy-1-cyclopentene and its methyl analogs, 1-aza-2-methoxy-1-cyclohexene and its methyl analogs, it was necessary to use low vacuum to remove the solvents in order to reduce the loss of these more volatile products. All ^1H NMR's are reported as δ values and were run in $CDCl_3$

1-Aza-2-methoxy-1-cyclopentene:

^1H NMR: 3.72 (s, OCH_3), 3.58 (t, $CH_2N=$),2.36 (t, $N=C-CH_2$), 1.94 (m).

1-Aza-2-methoxy-5-methyl-1-cyclopentene:

^1H NMR: 3.7 & 3.73 (2s, OCH_3), 3.85 (m, CHN=), 2.38 (m, $N=C-CH_2$); 2.14(m) & 1.42(m)(2H), 1.12 (d, $C-CH_3$).

1-Aza-2-methoxy-3-methyl-1-cyclopentene:

^1H NMR: 3.68 & 3.70 (2s, OCH_3), 3.38 & 3.60 (2t, $CH_2N=$), 2.13 & 2.58 (2m, N=C-CH), 1.40 (m), 1.16 (d, $C-CH_3$).

1-Aza-2-methoxy-1-cyclohexene:

^1H NMR: 3.55 (s, OCH_3), 3.40 (m, $CH_2N=$), 2.08 (m, $N=C-CH_2$), 1.48 & 1.64(m).

1-Aza-2-methoxy-3-methyl-1-cyclohexene:

^1H NMR: 3.51 (s, OCH_3), 3.35 (m, $CH_2N=$), 2.25 (m, $N=C-CH_2$), 1.34-1.74(m), 1.13 (d, $C-CH_3$).

1-Aza-2-methoxy-4-methyl-1-cyclohexene:

^{1}H NMR: 3.54 (s, OCH_3), 3.29 (m, CH_2N=), 2.15 (m, N=C-CH_2), 1.56-1.66 (m), 0.86 (d, C-CH_3).

1-Aza-2-methoxy-4-propyl-1-cyclohexene:

^{1}H NMR: 3.52 (br, OCH_3), 3.30 (m, CH_2N=), 2.16 (m, N=C-CH_2), 1.20-1.64 (m), 0.80 (t, C-CH_3).

1-Aza-2-methoxy-5-methyl-1-cyclohexene:

^{1}H NMR: 3.60 (b, OCH_3), 3.58 & 2.96 (2m, CH_2N=), 2.20 (m, N=C-CH_2), 1.32-1.77 (m), 0.92 (d, C-CH_3).

1-Aza-2-methoxy-5,5-dimethyl-1-cyclohexene:

^{1}H NMR: 3.62 (b, OCH_3), 3.17 (s, CH_2N=), 2.16 (t, N=C-CH_2), 1.47(t, CH_2), 0.90 (s, C-CH_3).

1-Aza-2-methoxy-3,5-dimethyl-1-cyclohexene:

^{1}H NMR: 3.52 (s, OCH_3), 2.86 (m, CH_2N=), 2.32 (m, N=C-CH_2), 1.46-1.72 (m, CH_2), 0.86(s, C-CH_3) 1.09 (s, C-CH_3).

1-Aza-2-methoxy-4-benzyl-1-cyclohexene:

^{1}H NMR: 3.61 (b, OCH_3), 3.36 (m, CH_2N=), 1.1-2.6(m).

1-Aza-2-methoxy-1-cycloheptene:

^{1}H NMR: 3.34(s, OCH_3), 3.26 (m, CH_2N=), 2.23 (m, N=C-CH_2), 1.37-1.60(m).

1-Aza-2-methoxy-1-cyclooctene:

^{1}H NMR: 3.56 (b, OCH_3), 3.34 (m, CH_2N=), 2.24 (m, N=C-CH_2), 1.3-1.6(m).

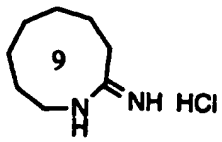
3,4-Dihydro-2-methoxyquinoline:

^{1}H NMR: 6.9-7.1 (m, aromatic H), 3.78 (s, OCH_3), 2.32 (t, CH_2N=), 2.73 (t, N=C-CH_2).

3,4,5,6-Tetrahydro-4-ethoxycarbonyl-2-methoxy-pyrazine:

^{1}H NMR: 4.15 (q, 2H), 3.90 (s, 2H), 3.65 (s, OCH_3), 3.42 (m, 2H), 2.50 (m, 2H), 1.22 (t,3H).

EXAMPLE 3



2-Imino-1-azacyclononane hydrochloride

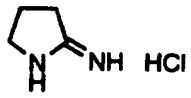
A mixture of 1-aza-2-methoxy-1-cyclononene (62 mg; 0.4 mmol) and ammonium chloride (20.5 mg; 0.4 mmol) in 1 mL of anhydrous ethanol was heated to reflux for 3 hours. The solvent was then removed *in vacuo* and the residue was triturated with Et2O to give almost a quantitative yield of 2-imino-1-azacyclononane hydrochloride as an amorphous solid.

^{1}H NMR($CDCl_3$): 8.7, 9.0 & 9.6 (3 br,NH's), 3.4 (m, CH_2N), 2.7 (m, CH_2C=N), 1.5-2.0(m).
Mass Spectrum m/e = 141

Note: In some cases a slight molar excess (5 - 10%) of the iminoether was used. The workup was effected by triturating the residual product with ethyl acetate or Et_2O. In specified cases the products were obtained as thick oils.

The following cyclic amidines (Examples 4-42) were synthesized according to the above general procedure by employing an appropriate iminoether instead of 1-aza-2-methyl-1-cyclononene and appropriate amine hydrochloride instead of ammonium chloride. All NMR's are reported as δ values.

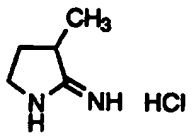
EXAMPLE 4



1-Aza-2-imino-cyclopentane hydrochloride:

^1H NMR($CDCl_3$): 9.44, 9.13 & 8.77 (3br, N-H's), 2.88 (t, CH_2N), 2.88 (t, $CH_2C{=}N$), 2.10(m).
Mass Spectrum m/e = 85 (M+1).

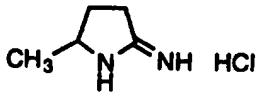
EXAMPLE 5



1-Aza-2-imino-3-methylcyclopentane hydrochloride:

^{1}H NMR($CDCl_3$): 9.48, 9.1 & 8.82 (3br, N-H's), 3.6-3.2 (m, CH_2N), 2.36 (t, CHC=N), 1.80 (m), 1.42 (d, C-CH3).
Mass Spectrum m/e = 99. (M+1).

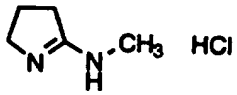
EXAMPLE 6



1-Aza-2-imino-5-methylcyclopentane hydrochloride:

^{1}H NMR($CDCl_3$): 9.5, 9.18 & 8.78 (3br, N-H's), 4.06 (t, CHN); 3.04-2.92 (m, CH_2C=N), 2.35 (m, CH_2), 1.32 (d,CCH_3).
Mass Spectrum m/e = 99 (M+1).

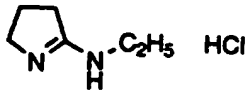
EXAMPLE 7



1-Aza-2-methylamino-1-cyclopentene hydrochloride: (oil)

^{1}H NMR ($CDCl_3$): 10.1 & 10.03 (2br, N-H's), 3.66 (b, CH_2N), 3.08 (d, N-CH_3), 2.91 (t, CH_2C=N), 2.12 (m).
Mass Spectrum m/e = 99 (M+1).

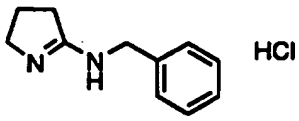
EXAMPLE 8



1-Aza-2-ethylamino-1-cyclopentene hydrochloride: (oil)

^{1}H NMR (D_6-DMSO): 10.13 & 9.9 (2br, N-H's), 3.7 (m, CH_2N), 3.58 (m, N-CH_3), 2.96 (m, CH_2C=N), 2.12 (m), 1.28 (t, CCH_3).
Mass Spectrum m/e = 113 (M+1).

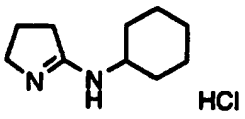
EXAMPLE 9



1-Aza-2-benzylamino-1-cyclopentene hydrochloride:

^{1}H NMR (D_6-DMSO): 10.16 (br,N-H's), 7.3-7.4 (m, aromatic H's), 4.54 (s, CH_2Ph), 3.56 (t, CH_2N), 2.84 (t, CH_2C=N), 2.06 (m).
Mass Spectrum m/e = 175 (M+1).

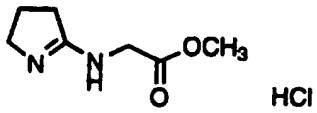
EXAMPLE 10



1-Aza-2-cyclohexylamino-1-cyclopentene hydrochloride.

^{1}H NMR (D_6-DMSO): 9.8 & 9.5 (2br, N-H's), 3.55 (t, CH_2N), 2.78 (t, CH_2C=N), 2.04 (m), 1.2-1.88(m).
Mass Spectrum m/e = 167 (M+1).

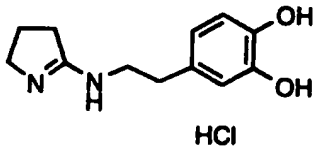
EXAMPLE 11



1-Aza-2-methoxycarbonylmethylamino-1-cyclopentene hydrochloride: (oil)

^{1}H NMR (D_6-DMSO): 10.0 (br, N-H's), 4.25 (s, -NCH_2COOMe), 3.7 (s, $COOCH_3$), 3.6 (t, CH_2N), 2.86 (t, $CH_2C{=}N$), 2.1(m).
Mass Spectrum m/e = 157 (M+1).

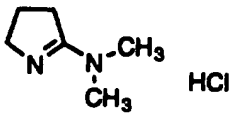
EXAMPLE 12



1-Aza-2-((3,4-dihydroxyphenyl)ethyl)amino-1-cyclopentene hydrochloride:

^{1}H NMR (D_6-DMSO): 9.5 (b,N-H's), 6.46-6.76 (m, aromatic H), 3.54 (t, CH_2), 3.36 (t, CH_2), 2.74 (t, CH_2), 2.02(m).
Mass Spectrum m/e = 221 (M+1).

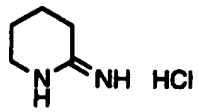
EXAMPLE 13



1-Aza-2,2-dimethylamino-1-cyclopentene hydrochloride.

^{1}H NMR($CDCl_3$): 11.24 (b, N-H's), 3.8 (t, CH2N), 3.4 (s, N-CH_3), 3.16 (t, CH2C=N), 2.86 (t, CH_2), 2.2(m).
Mass Spectrum m/e = 113 (M+1).

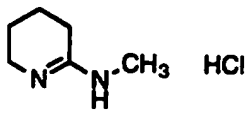
EXAMPLE 14



2-Iminopiperidine hydrochloride

Commercially available sample was used.

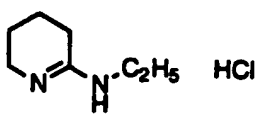
EXAMPLE15



1-Aza-2-methylamino-1-cyclohexene hydrochloride: (oil)

^{1}H NMR(D_6-DMSO): 9.3 & 9.22 (2br, NH's), 3.30 (m, CH_3), 2.78 (d, CH_3), 2.52 (m, CH_2C=N);1.70(m).
Mass Spectrum m/e = 113 (M+1).

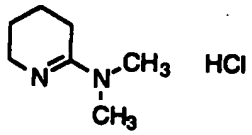
EXAMPLE 16



1-Aza-2-ethylamino-1-cyclohexene hydrochloride:

^{1}H NMR (D_6-DMSO): 9.3 (br, NH's), 3.28 (m, CH2N) 3.20 (m, CH_2N), 2.5 (m, CH_2C=N), 1.20 (t, CH_3).
Mass Spectrum m/e = 127 (M+1).

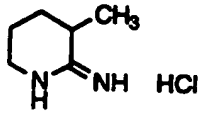
EXAMPLE 17



1-Aza-2-dimethylamino-1-cyclohexene hydrochloride.

^{1}H NMR ($CDCl_3$): 10.7 (br, NH's), 3.60 (m, CH_2N), 3.40 & 3.12 (2s, CH_3), 2.63-2.52 (m, CH_2), 1.85-1.77 (m).
Mass Spectrum m/e = 127 (M+1).

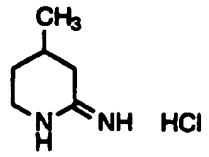
EXAMPLE 18



2-Imino-3-methylpiperidine hydrochloride:

^{1}H NMR (D_6-DMSO): 9.5 & 8.6 (2br,NH's), 3.25 (m, CH_2N), 2.7 (m, CHC=N), 1.4-1.9 (m), 1.25 (d, CH_3).
Mass Spectrum m/e = 113.1 (M+1).

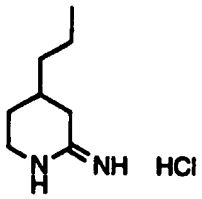
EXAMPLE 19



2-Imino-4-methylpiperidine hydrochloride:

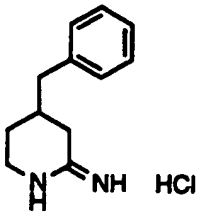
^{1}H NMR (D_6-DMSO): 9.5, 8.68 & 8.35 (3br, NH's), 3.24 (m, CH_2N), 2.55 & 2.15 (m, $CH_2C{=}N$), 1.35-1.85 (m), 0.96 (d,CH_3).
Mass Spectrum m/e = 113 (M+1).

EXAMPLE 20



2-Imino-4-propylpiperidine hydrochloride:
^{1}H NMR (D_6-DMSO): 9.5 & 8.7 (2br, NH's), 3.22 (m, CH_2N), 2.6-2.16 (m, $CH_2C{=}N$), 1.3-1.8(m), 0.85 (t, CH_3).
Mass Spectrum m/e = 141 (M+1).

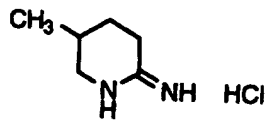
EXAMPLE 21



2-Imino-4-benzylpiperidine hydrochloride:

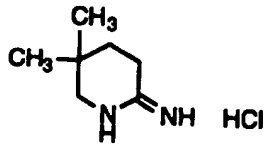
^{1}H NMR (D_6-DMSO): 9.54, 8.64 & 8.36 (3br, NH's), 7.15-7.35 (m, aromatic H), 3.35 & 3.2 (m, CH_2N), 2.6(m, $CH_2C{=}N$), 1.4-2.06(m).
Mass Spectrum m/e = 190 (M+1).

EXAMPLE 22



2-Imino-5-methylpiperidine hydrochloride:
^{1}H NMR (D_6-DMSO): 9.5, 8.7 & 8.4 (3br, NH's), 3.3 & 2.8 (m, CH_2N), 2.55 (m, $CH_2C{=}N$), 1.3-1.8 (m), 0.92 (d, CH_3).
Mass Spectrum m/e = 113 (M+1).

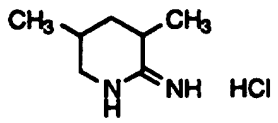
EXAMPLE 23



2-Imino-5,5-dimethylpiperidine hydrochloride:

^{1}H NMR (D_6-DMSO): 9.5 & 8.4 (2br, NH's), 2.95 (s, CH_2N), 2.52 (t, $CH_2C{=}N$), 1.48 (t, CH_2), 0.92 (d, CH_3).
Mass Spectrum m/e = 127 (M+1).

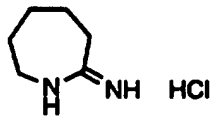
EXAMPLE 24



2-Imino-3,5-dimethylpiperidine hydrochloride:

^{1}H NMR (D_6-DMSO): 9.45, 8.7 & 8.5 (3br, NH's), 3.32 (m, CH_2N), 2.64 (m, CHC=N), 1.6-2.22(m).
Mass Spectrum m/e = 113 (M+1).

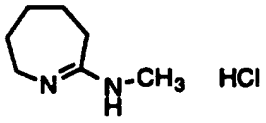
EXAMPLE 25



1-Aza-2-iminocycloheptane hydriochloride:

^{1}H NMR ($CDCl_3$): 9.5, 9.0 & 8.45 (3br,NH's), 3.4 (m, CH_2N), 2.75 (m, CH_2C=N), 1.4-1.8(m).
Mass Spectrum m/e = 127 (M+1).

EXAMPLE 26

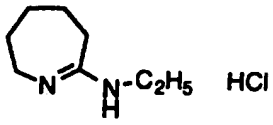


1-Aza-2-methylamino-1-cycloheptene hydrochloride:

^{1}H NMR ($CDCl_3$): 10.0 & 9.5 (2br, NH's), 3.50 (m, CH_2), 3.0 (d, CH_3), 2.8 (m, CH_2C=N), 1.6-1.84(m).

Mass Spectrum m/e = 127 (M+1).

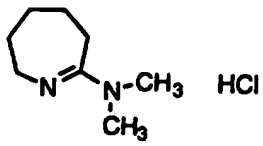
EXAMPLE 27



1-Aza-2-ethylamino-1-cycloheptene hydrochloride: (oil)

^{1}H NMR ($CDCl_3$): 9.8 & 9.54 (2br, NH's), 3.52 (m, CH_2), 2.85 (m, $CH_2C{=}N$), 1.70 (m), 1.3 (t, CH_3).
Mass Spectrum m/e = 141 (M+1).

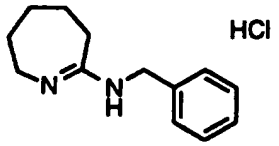
EXAMPLE 28



1-Aza-2-dimethylamino-1-cycloheptene hydrochloride.

^{1}H NMR ($CDCl_3$): 3.65 (m, CH_2N), 3.42 & 3.25 (2s, CH_3), 2.72 (m,CH_2), 1.6-1.85(m).
Mass Spectrum m/e = 141 (M+1).

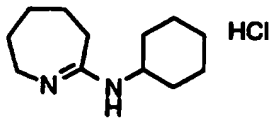
EXAMPLE 29



1-Aza-2-benzylamino-1-cycloheptene hydrochloride:

^{1}H NMR (D_6-DMSO): 9.9 & 9.6 (2br, NH's), 7.4 (m, aromatic H), 4.48 (b, CH_2), 3.45 (m, CH_2N), 2.76 (m, $CH_2C=N$), 1.5-1.75 (m).
Mass Spectrum m/e = 203 (M+1).

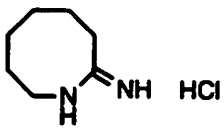
EXAMPLE 30



1-Aza-2-cyclohexylamino-1-cycloheptene hydrochloride.

1H NMR (D_6-DMSO): 9.2 (br, N-H's), 3.38 (m, CH_2N), 2.68 (t, $CH_2C=N$), 1.1-1.88 (m).
Mass Spectrum m/e = 195 (M+1).

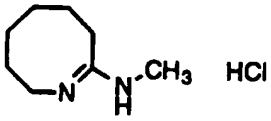
EXAMPLE 31



1-Aza-2-iminocyclooctane hydriochloride:

^{1}H NMR ($CDCl_3$): 9.6, 9.0 & 8.7 (3br, NH's), 3.45 (m, CH_2N), 2.7 (m, $CH_2C=N$), 1.5-2.0(m).
Mass Spectrum m/e = 127 (M+1).

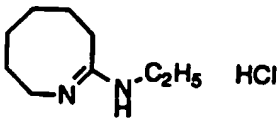
EXAMPLE 32



1-Aza-2-methylamino-1-cyclooctene hydrochloride:

^{1}H NMR ($CDCl_3$): 10.0 & 9.34 (2br, NH's), 3.55 (m,CH_2),3.05 (d, CH_3), 2.75 (m, $CH_2C=N$), 1.48-1.95(m).
Mass Spectrum m/e = 141 (M+1).

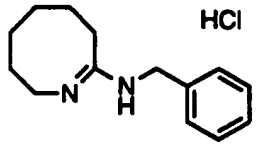
EXAMPLE 33



1-Aza-2-ethylamino-1-cyclooctene hydrochloride:

^{1}H NMR ($CDCl_3$): 8.2-10.0(br, NH's), 3.55 (m, CH_2), 2.5-2.76 (m, $CH_2C=N$), 1.26-2.05 (m), 1.3 (t, CH_3).
Mass Spectrum m/e = 155 (M+1).

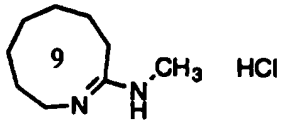
EXAMPLE 34



1-Aza-2-benzylamino-1-cyclooctene hydrochloride:

^{1}H NMR (D_6-DMSO): 9.9 & 9.3 (2br, NH's), 7.36 (m, aromatic H), 4.5 (b, CH_2), 3.5 (m, CH_2N), 2.7 (m, $CH_2C{=}N$), 1.3-1.75(m).
Mass Spectrum m/e = 217 (M+1).

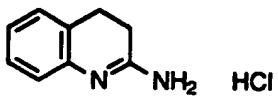
EXAMPLE 35



1-Aza-2-methylamino-1-cyclononene hydrochloride:

^{1}H NMR (D_6-DMSO): 9.64 & 8.95 (2br, NH's), 3.5 (m, CH_2), 3.05 (d, CH_3), 2.82 (d, CH_3), (2.64 (m, $CH_2C{=}N$), 1.25-1.8(m).
Mass Spectrum m/e = 155 (M+1).

EXAMPLE 36

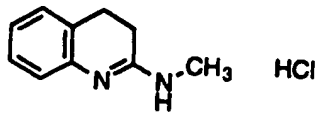


3,4-Dihydro-2-aminoquinoline hydrochloride:

^{1}H NMR (D_6-DMSO): 9.7 & 8.9 (2br, NH's), 7.1-7.3 (m, aromatic H), 2.9 (m, CH_2).

Mass Spectrum m/e = 147 (M+1).

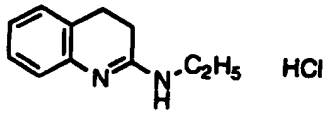
EXAMPLE 37



3,4-Dihydro-2-methylaminoquinoline hydrochloride:

^{1}H NMR (D_6-DMSO): 11.3 & 10.45 (2br, NH's), 7.1-7.5 (m, aromatic H), 3.1 (d, CH_3), 2.9 (CH_2).
Mass Spectrum m/e = 161 (M+1).

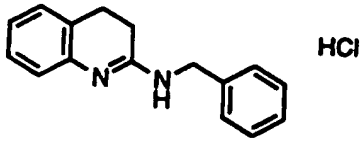
EXAMPLE 38



3,4-Dihydro-2-ethylaminoquinoline hydrochloride:

^{1}H NMR (D_6-DMSO): 10.4 (br, NH's), 7.1-7.5 (m, aromatic H), 3.58 (m, CH_2), 2.9 (CH_2), 1.25 (t, CH_3).
Mass Spectrum m/e = 175 (M+1).

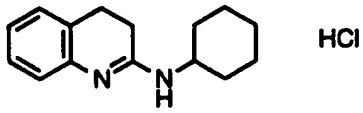
EXAMPLE 39



3,4-Dihydro-2-benzylaminoquinoline hydrochloride:

^1H NMR (D_6-DMSO): 10.75 (br, NH's), 7.1-7.55 (m, aromatic H), 4.86 (b, CH_2), 3.1 (d, CH_3), 2.95 (m, CH_2).
Mass Spectrum m/e = 237 (M+1).

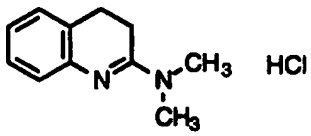
EXAMPLE 40



3,4-Dihydro-2-cyclohexylaminoquinoline hydrochloride:

^1H NMR (D_6-DMSO): 10.2 (br, NH's), 7.1-7.6 (m, aromatic H), 2.9 (CH_2), 1.1-2.0(m).
Mass Spectrum m/e = 229 (M+1).

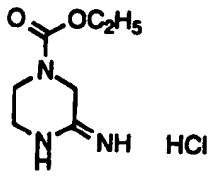
EXAMPLE 41



3,4-Dihydro-2-dimethylaminoquinoline hydrochloride:

^1H NMR (D_6-DMSO): 8.8 (br, NH's), 7.1-7.6 (m, aromatic H), 3.4 & 3.3 (2s, CH_3), 2.95(CH_2).
Mass Spectrum m/e = 175 (M+1).

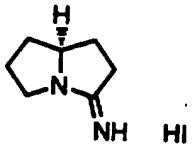
EXAMPLE 42



4-Ethoxycarbonyl-2-imino-piperazine hydrochloride:

^{1}H NMR (D6-DMSO): 9.1 & 8.8 (2br, NH's), 4.38 (br, CH_2), 4.1 (q, CH_2), 3.56 (br, CH_2), 3.35 (t, CH_2), 1.2 (t, CH_3).
Mass Spectrum m/e = 172 (M+1).

EXAMPLE 43



5-(S)-2-Imino-1-aza-bicyclo(3.3.0)octane hydroiodide

Step A: 1-t-butoxycarbonyl-2-(S)-pyrrolidinomethanol

To a vigourously stirring solution of 2.5 g (24.7 mmol) 2-(S)-pyrrolidinomethanol in 20 mL of saturated sodium bicarbonate solution at RT was added 6.25 mL (27.2 mmol) of di-*t*-butyl dicarbonate. Reaction was continued overnight at room temperature. Reaction mixture was diluted with water and extracted with EtOAc. EtOAc layer was washed with water, brine, dried, filtered and the filtrate was concentrated. Trituration of the white solid with hexane followed by filtration yielded 4.3 g of the desired compound.

^{1}H NMR (CDCl3): 4.76 (br s, 1H), 3.98 (br, 1H), 3.29-3.67 (m, 4H), 2.00-2.06(m, 1H), 1.78-1.84(m, 2H), 1.48 (s, 9H).

Step B: 1-t-Butoxycarbonyl-2-(S)-formyl-pyrrolidine.

To a solution of 0.44 mL (6.2 mmol) of DMSO in 3 mL of CH_2Cl_2 at -78 °C was added 0.36 mL (4.1 mmol) of Oxalyl chloride. After 10 min 0.402 g (2 mmol) of 1-t-butoxycarbonyl-2-(S)-pyrrolidinomethanol was added and stirred for 20 min. Triethylamine (1.7 mL, 12.4 mmol) was added to the reaction mixture and it was allowed to warm to room temperature. After stirring for 15 min at room temperature, the reaction was diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried and the filtrate was concentrated. The residue was chromatographed using 20% Et_2O-hexane to isolate 0.436 g (quantative) of the title compound mixed with a small amount of DMSO which was used in the next step.

Step C: 1-t-Butoxycarbonyl-2-(S)-methoxycarbonylethyl-pyrrolidine.

To a suspension of 0.16 g (4 mmol) of NaH in 10 mL of THF was added 0.73 mL (4 mmol) of methyl diethylphosphonoacetate. After 10 min a solution of 0.436 g (2 mmol) of 1-t-butoxycarbonyl-2-(S)-formyl-pyrrolidine prepared in step B was added. After stirring for 1 h the reaction was quenched by adding saturated NH4Cl and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried, concentrated and the residue was purified by chromatography using 20% EtOAc-hexane to furnish 0.383 g of oil.

^1H NMR ($CDCl_3$): 6.82 (dd, J= 15.5, 6 Hz, 1H), 5.83 (d, J= 15.5, 1H), 4.4 (m, 1H), 3.72 (s, 3H), 3.40 (m, 2H), 2.08 (m, 1H), 1.86 (m, 1H), 1.77 (m, 1H), 1.43 (s, 9H).

^{13}C NMR ($CDCl_3$ in ppm): 166.87, 148.84, 120.00, 57.81, 51.53, 46.18, 31.68, 28.35, 22.86.

A solution of 0.383 g of this oily product in 5 mL of methanol and 50 mg of 10 % Pd/C was stirred under H2 atmosphere overnight. The next morning the catalyst was filtered through a plug of

celite and the filtrate was concentrated to obtain 0.368 g (72%) of the title compound sufficiently pure for use in the next step.

^{1}H NMR ($CDCl_3$): 3.78(m, 1H), 3.65 (s, 3H), 3.28 (m, 2H), 2.32 (t, J=7.5 Hz, 2H), 1.45 (s, 9H).

Step D: 5-(S)-1-Aza-bicyclo(3.3.0)octan-2-one

A solution of 0.201 g (0.78 mmol) of 1-t-butoxycarbonyl-2-(S)-methoxycarbonylethyl-pyrrolidine in 3 mL of CH_2Cl_2 at 0 °C was treated with 1 mL of trifluoroacetic acid. During the next 1 h as the solution warmed to room temperature the reaction was complete. The reaction was concentrated and saturated K_2CO_3 solution was added to the residue until it was basic. The mixture was heated in a 75 °C for 18 h. The reaction was cooled and extracted with CH_2Cl_2 and the organic layer was washed with brine, dried and concentrated. The residue was chromatographed on a flash column using 10:45:45 mixture of MeOH:EtOAc:hexane to isolate 96 mg (98%) of the title compound.

^{1}H NMR ($CDCl_3$): 3.88 (m, 1H), 3.53 (m, 1H), 3.03 (m, 1H), 2.72 (m, 1H), 2.31 (m, 1H), 2.02-2.28 (m, 3H), 1.73 (m, 1H), 1.32 (m, 1H).
^{13}C NMR ($CDCl_3$ in ppm): 174.71, 62.04, 40.94, 35.35, 32.18, 27.15, 26.97.

Step E: 5-(S)-1-Aza-bicyclo(3.3.0)octan-2-thione

To a solution of 80 mg (0.64 mmol) of 5-(S)-1-aza-bicyclo(3.3.0)octan-2-one in 4 mL of toluene was added 0.388 g (0.96 mmol) of Lawesson's reagent and the mixture was heated in a 90 °C bath. After 18 h the reaction was cooled, concentrated and the residue was chromatographed using 20% EtOAc-hexane to furnish 83 mg (92%) of the title compound.

^{1}H NMR ($CDCl_3$): 4.17 (m, 1H), 3.72 (m, 1H), 3.40-3.23 (m, 3H), 2.38-2.21 (m, 4H), 1.78 (m, 1H), 1.47 (m, 1H).
^{13}C NMR ($CDCl_3$ in ppm): 69.68, 49.36, 44.56, 31.60, 29.36, 27.50.

Step F: 5-(S)-2-Imino-1-aza-bicyclo(3.3.0)octane. hydroiodide

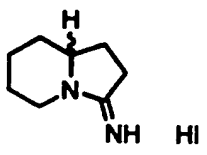
Methyl iodide (1.5 mL) was added to 83 mg (0.59 mmol) of 5-(S)-1-aza-bicyclo(3,3,0)octan-2-thione and the mixture was stirred overnight. Next morning excess methy iodide was removed in vacuo leaving a solid residue.

^{1}H NMR (D_2O): 4.66 (m, 1H), 3.53 (m, 1H), 3.68-3.57 (m, 4H), 2.76 (s, 3H), 2.53-2.41 (m, 3H), 2.26 (m, 1H), 2.03 (m, 1H), 1.66 (m, 1H).
^{13}C NMR (D_2O in ppm): 187.28, 75.86, 45.84, 43.19, 29.53, 27.52, 27.05, 15.40.

The solid obtained from the above reaction was dissolved in 5 mL of MeOH and the solution was saturated with NH_3. After stirring for 18 h the reaction mixture was concentrated leaving a white solid residue. The solid was triturated with ether and dried to isolate 0.161 g (quantative) of the title compound as a hydroiodide salt.

^{1}H NMR (D_2O): 4.31 (m, 1H), 3.40 (m, 2H), 3.25 (m, 1H), 3.04 (m, 1H), 2.36-2.27 (m, 4H), 1.94 (m, 1H), 1.53 (m, 1H).
^{13}C NMR (D_2O in ppm): 165.37, 69.08, 49.03, 42.66, 35.96, 30.38, 27.83, 27.18.

EXAMPLE 44



2-Imino-1-aza-bicyclo(4.3.0)nonane hydroiodide

Step A: 1-t-butoxycarbonyl-2-(R+S)-piperidinodinomethanol

Starting from 5 gm (43.4 mmol) of 2-(R+S)-piperidinodinomethanol and following the procedure as in example 43, step A gave 7.06 gm of the title product.

^{1}H NMR ($CDCl_3$): 4.26 (m, 1H), 3.92 (m, 1H), 3.77(m, 1H), 3.59 (m, 1H), 2.84 (m, 1H), 1.49-1.60 (m, 3H), 1.44 (s, 9H).
^{13}C NMR ($CDCl_3$ in ppm): 79.72, 61.40, 52.37, 39.95, 33.88, 28.37, 25.19, 25.11, 19.50.

Step B: 1-t-Butoxycarbonyl-2-(R+S)-formyl-piperidine

Starting from 0.7 gm (3.2 mmol) of1-t-butoxycarbonyl-2-(R+S)-piperidinodinomethanol and following the procedure as in example 43, step B, gave 0.675 gm of the desired compound.

^{1}H NMR ($CDCl_3$): 9.60 (d, J=5.7 Hz, 1H), 4.55 (br s,1H), 3.95 (br s, 1H), 2.94 (br s, 1H), 2.17 (m, 1H), 1.67-1.28 (m, 5H), 1.48 (s, 9H).

Step C: 1-t-Butoxycarbonyl-2-(R+S)-methoxycarbonylethyl-piperidine

To a suspension of 0.088 g (3.7 mmol) of NaH in 5 mL of THF was added 0.68 mL (4 mmol) of methyl diethylphosphonoacetate at -10°C. After 10 min a solution of 0.528 g (2.47 mmol) of 1-t-butoxycarbonyl-2-(R+S)-formyl-piperidine prepared in step B was added. After stirring for 1 h the reaction was quenched by adding saturated NH_4Cl and extracted with EtOAc. The EtOAc layer was washed with brine, dried, concentrated and the residue was purified by chromatography using 5% EtOAc-hexane to furnish 0.579 g of oil.

^{1}H NMR ($CDCl_3$): 6.88 (m, 1H), 5.81 (d, J= 15.8, 1H), 4.94 (m, 1H), 3.98 (m, 2H), 3.74 (s, 3H), 2.81 (m, 1H), 1.81-1.60 (m, 5H), 1.45 (s, 9H).
^{13}C NMR ($CDCl_3$ in ppm): 166.61, 154.94, 121.56, 79.79, 51.53, 28.89, 28.33, 25.22, 19.81.

A solution of 0.570 g of this oily product in 5 mL of methanol and 50 mg of PtO_2 was stirred under H_2 atmosphere overnight. The next morning the catalyst was filtered through a plug of celite and the filtrate was concentrated to obtain 0.548 g of the title compound sufficiently pure for use in the next step.

^{1}H NMR ($CDCl_3$): 4.24(m, 1H), 3.66 (s, 3H), 2.73 (m, 1H), 2.31-2.25 (m, 2H), 2.13-2.07 (m, 1H), 1.69-1.50 (m, 6H 1.45 (s, 9H).
^{13}C NMR ($CDCl_3$ in ppm): 174.00, 154.96, 79.20, 51.49, 49.88, 30.89, 28.85, 28.37, 28.27, 25.50, 24.96, 19.01.

Step D: 5-(R+S)-1-Aza-bicyclo(4.3.0)nonan-2-one

A solution of 0.548 g (2.02 mmol) of 1-t-butoxycarbonyl-2-(R+S)-methoxycarbonylethyl-piperidine in 3 mL of CH_2Cl_2 at 0 °C was treated with 1 mL of trifluoroacetic acid. During the next 1 h as the solution warmed to room temperature the reaction was complete. The reaction was concentrated and saturated K_2CO_3 solution was added to the residue until it was basic. The mixture was heated in a 75 °C for 2 h. The reaction was cooled and extracted with CH_2Cl_2 and the organic layer was washed with brine, dried and concentrated. The residue was chromatographed on a flash column using 10:45:45 mixture of MeOH:EtOAc:hexane to isolate 0.187 g (67%) of the title compound.

^{1}H NMR ($CDCl_3$): 4.04 (m, 1H), 3.34 (m, 1H), 2.54 (m, 1H), 2.27 (m, 1H), 2.14 (m, 1H), 1.80 (m, 2H), 1.63 (m, 1H), 1.50 (m, 1H), 1.36-1.23 (m, 2H), 1.09 (m, 1H).
^{13}C NMR ($CDCl_3$ in ppm): 173.47, 57.17, 40.11, 33.48, 30.20, 25.23, 24.35, 23.58.

Step E: 5-(R+S)-1-Aza-bicyclo(4.3.0)nonan-2-thione

To a solution of 90 mg (0.64 mmol) of 5-(R+S)-1-aza-bicyclo(4.3.0)nonan-2-one in 4 mL of toluene was added 0.392 g (0.97 mmol) of Lawesson's reagent and the mixture was heated in a 90 ^{o}C bath. After 18 h the reaction was cooled, concentrated and the residue was chromatographed using 70% CH2Cl2-hexane to furnish 95 mg (96%) of the title compound.

^{1}H NMR ($CDCl_3$): 4.85 (m, 1H), 3.71 (m, 1H), 3.05 (m,1H), 2.94 (m, 1H), 2.83 (m, 1H), 2.26 (m, 1H), 2.00 (m, 1H), 1.89 (m, 1H), 1.83 (m, 1H), 1.65 (m, 1H), 1.53-1.42 (m, 2H), 1.28 (m, 1H).
^{13}C NMR ($CDCl_3$ in ppm): 199.15, 65.13, 45.53, 43.40, 33.34, 26.66, 24.23, 22.99.

Step F: 5-(R+S)-2-Imino-1-aza-bicyclo(4.3.0)nonane.hydroiodide

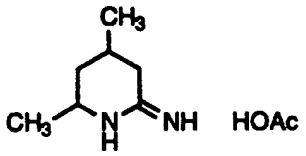
Methyl iodide (1 mL) was added to 50 mg (0.32 mmol) of 5-(R+S)-1-aza-bicyclo(4.3.0)nonan-2-thione and the mixture was stirred for 5 hr. Excess methy iodide was removed in vacuo leaving a solid residue.

^{1}H NMR (D_2O): 4.20 (m, 1H), 4.07 (m, 1H), 3.45-3.26 (m, 3H), 2.74(s, 3H), 2.51 (m, 1H), 2.11 (m, 1H), 1.90 (m, 2H), 1.58-1.49 (m, 3H).
^{13}C NMR (D_2O in ppm): 70.41, 48.57, 37.01, 32.30, 25.43, 23.66, 21.73, 14.91.

The solid obtained from the above reaction was dissolved in 5 mL of MeOH and the solution was saturated with NH_3. After stirring for 18 h the reaction mixture was concentrated leaving a white solid residue. The solid was triturated with ether and dried to isolate 83 mg (quantative) of the title compound as a hydroiodide salt.

^{1}H NMR (D_2O): 3.84-3.78 (m, 2H), 3.07 (m, 1H), 2.85 (m, 2H), 2.32(m, 1H), 2.01 (m, 1H), 1.86-1.72 (m, 4H), 1.48 (m, 2H), 1.34 (m, 1H).
^{13}C NMR (D_2O in ppm): 166.27, 63.61, 43.14, 31.94, 29.93, 25.30, 23.30, 21.97.

EXAMPLE 45



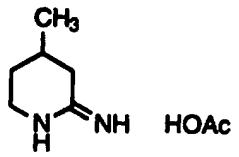
cis-4,6-Dimethyl-2-imino-piperidine, acetic acid salt.

2-Amino-4,6-dimethyl-pyridine (2.00 g, 16.4 mmol) was dissolved in 10.0 mL of glacial acetic acid and 0.90 g of 5% rhodium on alumina was added. The mixture was shaken under a hydrogen atmosphere at 40 psi for 16 h. After filtering the mixture through Celite and washing the catalyst with an additional 25 mL of acetic acid, the filtrate was concentrated to a weight of 4.5 g. Toluene (3x10 mL) and then ethyl acetate (20 mL) were added sequentially, with evaporation of the solvent under vacuum following the addition of each portion. The residue was dissolved in methanol and filtered through a 0.45 micron membrane. The filtrate was evaporated and the residue was dissolved in 20 mL of ethyl acetate and cooled to 0 °C. Filtration and drying under vacuum yielded 958 mg (31% yield) of *cis*-4,6-dimethyl-2-imino-piperidine, acetic acid salt.

^{1}H-NMR (400 MHz, CD_3OD) δ 3.58 (m, 1H), 2.62 (ddd, 1H, J = 17.5, 4.5, 2 Hz), 2.16 (ddd, J = 17.5, 12, 1.5 Hz), 2.00-1.90 (m, 2H), 1.89 (s, 3H), 1.27 (d, 3H, J = 6 Hz), 1.11 (q, 1H, J = 12 Hz), 1.06 (d, 3H, J = 6 Hz).
Mass spectrum: 127 (M+1).

Following the above procedures, the following 2-iminopiperidines (Examples 46-59) were synthesized from the appropriate 2-aminopyridine:

EXAMPLE 46

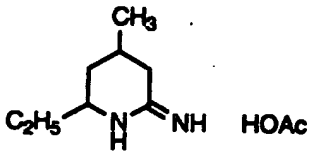


2-Imino-4-methyl-piperidine, acetic acid salt

^{1}H-NMR (400 MHz, CD_3OD) δ 3.24 (ddd, 1H, J = 13, 5.5, 2.5 Hz), 3.14 (ddd, 1H, J = 13, 10, 5 Hz), 2.45 (ddd, 1H, J = 17.5, 5, 1.5 Hz), 2.04 (dd, J = 17.5, 10 Hz), 1.88-1.68 (m, 2H), 1.64 (s, 3H), 1.30 (dtd, 1H, J = 13, 10, 5.5 Hz), 0.95 (d, 3H, J = 6 Hz).

Chemical Analysis. Calc. for $C_8H_{16}N_2O_2$: 55.79% C, 9.36% H, 16.27% N. Found: 55.95% C, 9.29% H, 16.33% N.

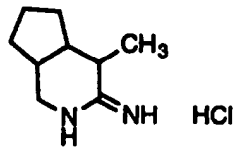
EXAMPLE 47



6-Ethyl-2-imino-4-methyl-piperidine, acetic acid salt.

^{1}H-NMR (400 MHz, CD_3OD) δ 3.48-3.39 (m, 1H), 2.63 (ddd, 1H, J = 17.5, 4.5, 2 Hz), 2.17 (ddd, 1H, J = 17.5, 12, 1.5 Hz), 2.03-1.90 (m, 2H), 1.90 (s, 3H), 1.69 (dqd, J = 14, 7, 5 Hz), 1.56 (dq, J = 14, 7 Hz), 1.10 (q, J = 12 Hz), 1.07 (d, 3H, J = 7 Hz), 0.98 (t, J = 7 Hz).

EXAMPLE 48

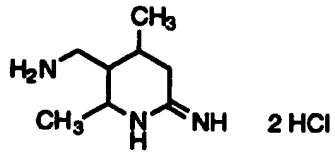


4-Imino-5-*cis*-methyl-3-azabicyclo [4.3.0] nonane. hydrochloride.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42 (dm, 1H, J=13Hz), 3.23 (d, 1H, J=13Hz), 2.84-2.87 (m,1H), 2.62-2.49 (1H, m), 2.02-1.95 (1H, m), 1.93-1.86 (1H, m), 1.76-1.69 (1H, m), 1.41-1.28 (2H, m), 1.249 (3H, d, J=7Hz), 0.95-0.86 (1H, m).

Mass spectrum m/e = 153 (M+1).

EXAMPLE 49

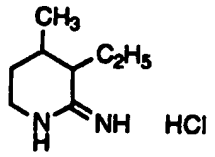


cis-5-Aminomethyl-4,6-dimethyl-2-imino-piperidine. dihydrochloride.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95-3-88 (m, 1H), 3.05(t, 2H, J=5Hz), 2.73 (dd, 1H, J=17Hz, J=5.5Hz), 3.05 (t, 2H J=4.5 Hz), 2.73 (dd, 1H, J=18Hz, J=5.5Hz), 2.37 (dd, 1H, J=18Hz, J=9.5Hz), 2.4-2.3 (m, 1H), 2.25-2.20 (m, 1H,), 1.37 (d, 3H, J=7.1Hz), 1.15 (d, 3H, J=6.7Hz).

Mass spectrum m/e = 156 (M+1).

EXAMPLE 50

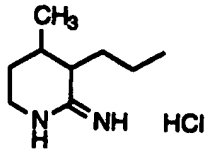


cis-3-Ethyl-2-imino-4-methyl-piperidine, hydrochloride.

^{1}H NMR (500 MHz, CD_3OD) δ 3.44 (m, 1 H), 3.38 (m, 1 H), 2.48 (dd, J = 4 Hz, 1 H), 2.16 (m, J = 10 & 4 Hz, 1 H), 1.83 (m, 1 H), 1.74 (m, 2 H), 1.67 (m, 1 H), 1.06 (t, J = 8 Hz, 3 H), 1.05 (d, J = 7 Hz, 3 H).

Mass spectrum m/e = 141

EXAMPLE 51

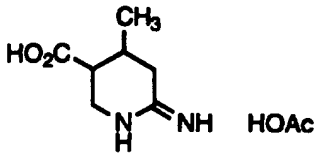


cis-2-Imino-4-methyl-3-n-propyl-piperidine, hydrochloride.

^{1}H NMR (500 MHz, CD_3OD) δ 3.44 (m, 1 H), 3.38 (m, 1 H), 2.55 (dd, J = 5 Hz, 1 H), 2.15 (m, J = 10 & 4 Hz, 1 H), 1.83 (m, 1 H, H_5), 1.76 (m, 1 H), 1.59 (m, 2 H), 1.45 (m, 2 H), 1.05 (d, J = 7 Hz, 3 H), 0.99 (t, J = 7 Hz, 3 H).

Mass spectrum m/e = 155

EXAMPLE 52

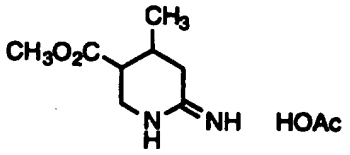


cis/trans-2-Imino-4-methyl-piperidine-5-carboxylic acid, acetic acid salt.

^{1}H NMR (400 MHz, CD_3OD) δ 1.04 (d, 1.5H), 1.08 (d, 1.5H).

Mass spectrum m/e = 156 (M).

EXAMPLE 53

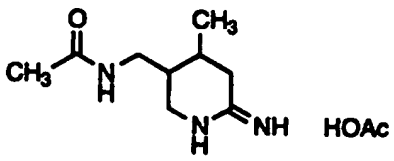


cis/trans-2-Imino-4-methyl-piperidine-5-carboxylic acid, methyl ester, acetic acid salt.

^{1}H NMR (400 MHz, CD_3OD) δ 1.05 (d, 1.5H), 1.09 (d, 1.5H), 3.74 (d, 3H).

Mass spectrum m/e = 171 (M+1).

EXAMPLE 54

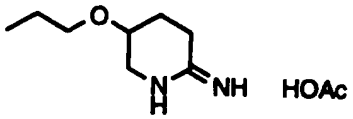


cis/trans-5-Acetamidomethyl-2-imino-4-methyl-piperidine, acetic acid salt.

^{1}H NMR (400 MHz, CD_3OD) δ 1.02 (d, 1.5H), 1.10 (d, 1.5H).

Mass spectrum m/e = 184 (M+1).

EXAMPLE 55

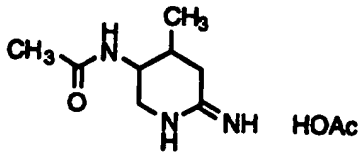


2-Imino-5-n-propyloxy-piperidine, acetic acid salt.

^{1}H NMR (400 MHz, CD_3OD) δ 0.95 (t, 3H), 1.59 (m, 2H).

Mass spectrum m/e = 157 (M+1).

EXAMPLE 56

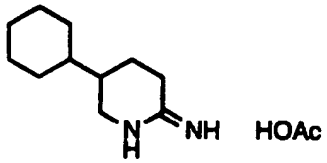


cis/trans-5-Acetamido-2-imino-4-methyl-piperidine, acetic acid salt.

^{1}H NMR (400 MHz, CD_3OD) δ 1.00 (d, 1.5H), 1.05 (d, 1.5H), 1.97 (d, 3H).

Mass spectrum m/e =170 (M+1).

EXAMPLE 57

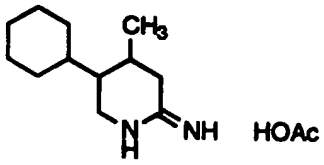


5-Cyclohexyl-2-imino-piperidine, acetic acid salt.

^{1}H NMR (400 MHz, CD_3OD) δ 1.00-1.85 (br m, 11H).

Mass spectrum m/e = 181 (M+1).

EXAMPLE 58

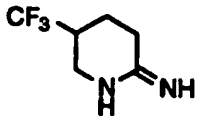


cis/trans-5-Cyclohexyl-2-imino-4-methyl-piperidine, acetic acid salt.

^{1}H NMR (400 MHz, CD_3OD) δ 0.90 (d, 1.5H), 1.05 (d, 1.5H).

Mass spectrum m/e = 195 (M+1).

EXAMPLE 59

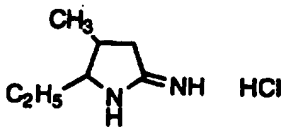


2-Imino-5-trifluoro-piperidine..acetic acid salt

^{1}H NMR (400MHz, CD_3OD) δ 1.83-1.97 (br m, 1H), 2.14-2.20 (br m, 1H), 2.74-2.80 (br m, 2H), 2.86-3.00 (br m, 1H), 3.337-3.44 (m, 1H), 3.62-3.68 (q, 1H).

Mass spectrum m/e = 167 (M+1).

EXAMPLE 60



2-Imino-5-ethyl-4-methylpyrrolidine hydrochloride

Step A: Methyl 3-methyl-4-nitrohexanoate

A solution of 4 g (40 mmol) of methyl crotonate and 4.72 g (53 mmol) of 1-nitropropane in 20 mL of acetonitrile was treated with 6 mL (40 mmol) of 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU). After stirring for 22 h at room temperature the reaction mixture was diluted with water and acidified with 2 N HCl. The solution was extracted with Et_2O and the Et_2O layer was washed with brine, dried and concentrated. The residue was chromatographed on a flash column using 10 % Et_2O-Hexane to isolate 6.41 g (85%) of the title compound.

^{1}H NMR ($CDCl_3$, since stereoisomers were present multiple peaks were observed and ppm ranges are given): 4.44 & 4.38 (2m, 1H), 3.70 & 3.69 (2s, 3H), 2.65-1.7 (m, 5H), 1.06 & 1.01 (2d, 3H, J=7 Hz), 0.97 (t, 3H, J=7 Hz).

Step B: 5-Ethyl-4-methyl-2-pyrrolidone

A solution of 4.0 g (21 mmol) of methyl 3-methyl-4-nitrohexanoate (from step A) in 20 mL of EtOH containing 0.4 g of PtO2 was hydrogenated on a Parr apparatus for 3 days. The catalyst was filtered and washed with EtOH and the filtrate was concentrated. Vacuum distillation of the residue furnished 1.6 g (61%) of the title compound: bp 102-107 °C/2 mm.

^{1}H NMR ($CDCl_3$, since stereoisomers were present multiple peaks were observed and ppm ranges are given): 6.9 (br s, 1H), 3.50 & 3.11 (2 m, 1 H), 2.65-1.3 (m, 5H), 1.14 & 1.04 (2d, 3H, J=7 Hz), 0.96 (t, 3H, J=7 Hz).

Step C: 1-aza-5-ethyl-2-methoxy-4-methyl-1-cyclopentene

To a solution of 0.254 g (2 mmol) of 5-ethyl-4-methyl-2-pyrrolidone (from step B) in 3 mL of CH_2Cl_2 was added 0.355 g (2.4 mmol) of trimethyloxonium tetrafluoroborate under a N2 atmosphere. After stirring overnight the reaction mixtrue was quenched with saturated K_2CO_3 solution and diluted with Et_2O. The solution was filtered and the filtrate was concentrated. The residue was purified by flash chromatography using Et_2O-hexane to isolate 0.224 g (79%) of the title compound.

^{1}H NMR ($CDCl_3$, since stereoisomers were present multiple peaks were observed and ppm ranges are given): 3.8 (s, 3H), 3.6-3.4 (m, 1 H), 2.7-0.8 (m, 10H).

Step D: 2-Imino-5-ethyl-4-methylpyrrolidine hydrochloride

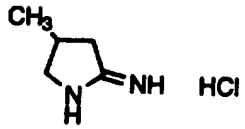
A mixture of 0.1 g (0.71 mmol) in 3 mL of EtOH containing 0.03 g (0.56 mmol) of NH_4Cl was heated to reflux. After 4 h the solution was cooled and concentrated and the residue was suspended in EtOAc. The precipateted solid was filtered washed with EtOAc and dried to furnish 0.072 g (79%) of the title compound.

^{1}H NMR (D_2O, since stereoisomers were present multiple peaks were observed and ppm ranges are given): 3.82 & 3.50 (2 q, 1H), 3.1-2.45 (m, 2 H), 2.31 & 1.64 (2 m, 1H), 1.6-1.45 (m, 2H), 1.11 & 1.0 (2 d, 3H, J=7 Hz), 0.92 (t, 3H, J=7 Hz).

Mass spectrum m/e = 127 (M+1)

The following 2-imino-pyrrolidines (Examples 61-78) were prepared by the method of Example 60 by substituting appropriate nitroalkane and acrylate esters.

EXAMPLE 61

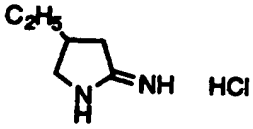


2-Imino-4-methylpyrrolidine hydrochloride

^{1}H NMR (D_2O): 3.73 (t, 1H), 3.22 (dd, 1H), 2.97 (dd, 1H), 2.65 (m, 1H), 2.47 (dd, 1H), 1.08 (d, 3H).

Mass spectrum m/e = 99 (M+1)

EXAMPLE 62

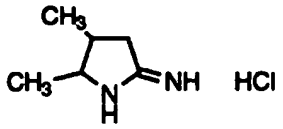


2-Imino-4-ethylpyrrolidine hydrochloride

^{1}H NMR (D_2O): 3.75 (dd, 1H), 3.31 (dd, 1H), 2.98 (q, 1H), 2.54 (m, 2H), 1.49 (m, 2H), 0.89 (t, 3H).

Mass spectrum m/e = 113 (M+1)

EXAMPLE 63

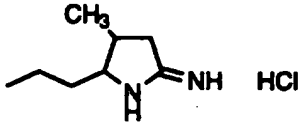


2-Imino-4,5-dimethylpyrrolidine hydrochloride

^{1}H NMR (D_2O, since stereoisomers were present multiple peaks were observed and ppm ranges are given): 4.05 & 3.69 (2 m, 1H), 2.99 & 2.94 (2 dd, 1 H), 2.66 & 2.17 (2m, 1H), 2.54 & 2.51 (2t, 1H), 1.25, 1.13, 1.1 & 0.99 (4d, 6H).

Mass spectrum m/e = 113 (M+1)

EXAMPLE 64

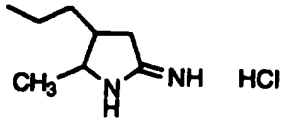


2-Imino-4-methyl-5-propylpyrrolidine hydrochloride

^{1}H NMR (D_2O, since stereoisomers were present multiple peaks were observed and ppm ranges are given): 3.69 & 3.30 (2 q, 1H), 1.95- 2.6 (m, 3 H), 1.2-1.6 (m, 4H), 1.08 & 0.96 (2 d, 3H), 0.90 (t, 3H).

Mass spectrum m/e = 142 (M+1)

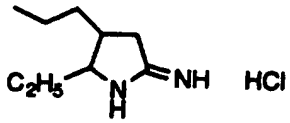
EXAMPLE 65



2-Imino-5-methyl-4-propylpyrrolidine hydrochloride

Mass spectrum m/e = 141 (M+1)

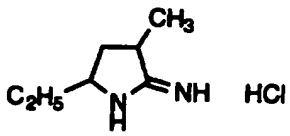
EXAMPLE 66



2-Imino-5-ethyl-4-propylpyrrolidine hydrochloride

Mass spectrum m/e = 155 (M+1)

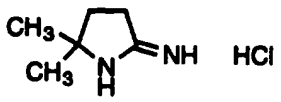
EXAMPLE 67



2-Imino-5-ethyl-3-methylpyrrolidine hydrochloride

Mass spectrum m/e = 127 (M+1)

EXAMPLE 68

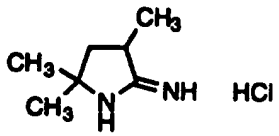


2-Imino-5,5-dimethylpyrrolidine hydrochloride

^{1}H NMR (D_2O): 2.91 (t, 2H), 2.04 (t, 2H), 1.33 (s, 6H).

Mass spectrum m/e = 113 (M+1)

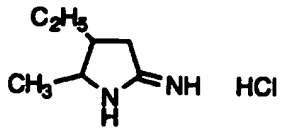
EXAMPLE 69



2-Imino-3,5,5-trimethylpyrrolidine hydrochloride

Mass spectrum m/e = 127 (M+1)

EXAMPLE 70

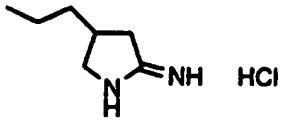


2-Imino-4-ethyl-5-methylpyrrolidine hydrochloride

^{1}H NMR (D_2O, since stereoisomers were present multiple peaks were observed and ppm ranges are given): 4.08 & 3.71 (2 m, 1H), 3.1-2.4 (m, 3 H), 1.6-1.2 (m, 2H), 1.26 & 1.11 (2 d, 3H), 0.90 (t, 3H).

Mass spectrum m/e = 127 (M+1)

EXAMPLE 71

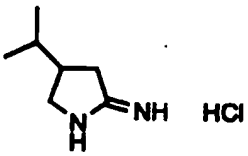


2-Imino-4-propylpyrrolidine hydrochloride

^{1}H NMR (D_2O): 3.74 (dd, 1H), 3.30 (dd, 1 H), 2.97 (dd, 1H), 2.6 (m, 2H), 1.45 (q,2H), 1.31 (m, 2H), 0.88 (t, 3H).

Mass spectrum m/e = 127 (M+1)

EXAMPLE 72

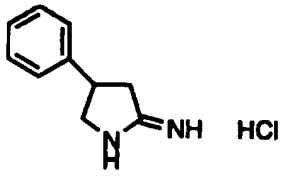


2-Imino-4-(2-methyl-ethyl)pyrrolidine hydrochloride

^{1}H NMR (D_2O): 3.72 (t, 1H), 3.37 (dd, 1 H), 2.91 (dd, 1H), 2.63 (dd, 1H), 2.39 (m, 1H), 1.66 (m, 1H), 0.88 (2d, 6H).

Mass spectrum m/e = 127 (M+1)

EXAMPLE 73

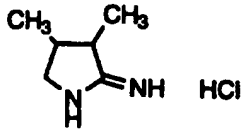


2-Imino-4-phenylpyrrolidine hydrochloride

^{1}H NMR (D_2O): 7.4 (m, 2H), 7.32 (m, 3H), 4.02 (dd, 1H), 3.82 (m, 1H), 3.62 (m, 1H), 3.25 (dd, 1H), 2.97 (dd, 1H).

Mass spectrum m/e = 161 (M+1)

EXAMPLE 74

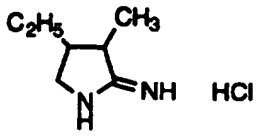


2-Imino-3,4-dimethylpyrrolidine hydrochloride

^{1}H NMR (D_2O, since stereoisomers were present multiple peaks were observed): 3.74 & 3.68 (2 dd, 1H), 3.25 & 3.19 (2 dd, 1 H), 3.12 & 2.23 (2 m, 1H), 2.68 (m, 1H), 1.27 & 1.17 (2 d, 3H,), 1.12 & 1.0 (2 d, 3H).

Mass spectrum m/e = 113 (M+1)

EXAMPLE 75

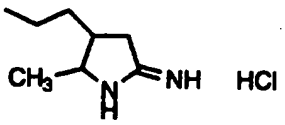


2-Imino-4-ethyl-3-methylpyrrolidine hydrochloride

^{1}H NMR (D_2O, since stereoisomers were present multiple peaks were observed and ppm ranges are given): 3.77 & 3.67 (2 t, 1H), 3.32 & 3.26 (2t, 1 H), 1.6-3.1(m, 2H), 1.51 & 1.40 (2m, 2H), 1.29 & 1.17 (2 d, 3H,), 0.90 (m, 3H).

Mass spectrum m/e = 127 (M+1)

EXAMPLE 76

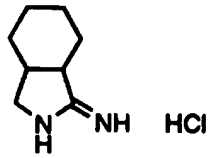


2-Imino-5-methyl-4-propylpyrrolidine hydrochloride

^{1}H NMR (D_2O, since stereoisomers were present multiple peaks were observed and ppm ranges are given): 3.82 & 3.50 (2 q, 1H), 2.45- 3.1 (m, 2 H), 2.31 & 1.64 (2 m, 1H), 1.45-1.6 (m, 2H), 1.11 & 1.0 (2 d, 3H, J=7 Hz), 0.92 (t, 3H, J=7 Hz).

Mass spectrum m/e = 127 (M+1)

EXAMPLE 77

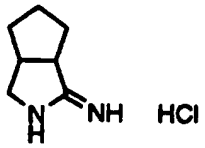


2-Imino-3-azabicyclo(4.3.0)nonane hydrochloride

^{1}H NMR (D_2O): 3.56 (dd, 1H), 3.32 (dd, 1 H), 3.02 (q, 1H), 2.56 (q, 1H), 1.2-2.0 (m, 8H).

Mass spectrum m/e = 139 (M+1)

EXAMPLE 78



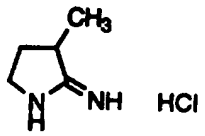
2-Imino-3-azabicyclo(3.3.0)octane hydrochloride

^{1}H NMR (D_2O): 3.82 (dd, 1H), 3.48 (dt, 1 H), 3.32 (dd, 1H), 2.98 (m, 1H), 1.4-2.1(m, 6H).

Mass spectrum m/e = 125 (M+1)

The compounds of examples 79 and 80 were synthesized from the commercially available pyrrolidone intermediates by the procedure outlined in step C and D in example 60.

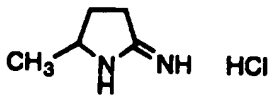
EXAMPLE 79



2-Imino-3-methylpyrrolidine hydrochloride

^{1}H NMR (D_2O): 9.48 (s, 1H), 9.1 (s, 1H), 8.82 (s, 1H), 3.6 (m, 1H), 3.28 (m, 1H), 2.37 (m, 1H), 1.78 (m, 1H), 1.40 (d, 3H).

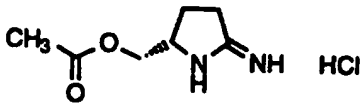
EXAMPLE 80



2-Imino-5-methylpyrrolidine hydrochloride

^{1}H NMR (D_2O): 9.49 (s, 1H), 9.18 (s, 1H), 8.79 (s, 1H), 4.05 (m, 1H), 3.02 (m, 1H), 2.92 (m, 1H), 2.33 (m, 1H), 1.73 (m, 1H), 1.32 (d, 3H).

EXAMPLE 81

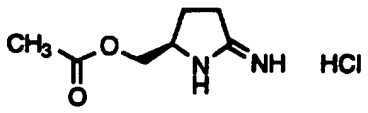


2-Imino-5-(S)-acetyloxymethylpyrrolidine hydrochloride

The commercially available (S) 5-(hydroxymethyl)-2-pyrrolidone was acylated with acetic anhydride and the product was subjected to the procedure of Example 60, steps C and D to isolate the title compound.

^{1}H NMR (D_2O): 4.28 (m, 2H), 4.07 (m, 1 H), 2.92 (m, 2H), 2.37 (m, 1H), 2.11 (s, 3H), 2.0 (m, 1H).

EXAMPLE 82



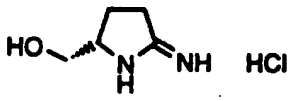
2-Imino-5-(R)-acetyloxymethylpyrrolidine hydrochloride

The title compound was prepared by the procedure of example 81 starting from (R) 5-(hydroxymethyl)-2-pyrrolidone.

^{1}H NMR (D_2O): 4.3(m, 2H), 4.09 (q, 1 H), 2.92 (m, 2H), 2.39 (m, 1H), 2.10 (s, 3H), 2.0 (m, 1H).

Mass spectrum m/e = 157 (M+1)

EXAMPLE 83



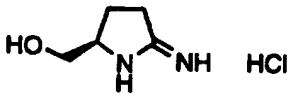
2-Imino-5-(S)-hydroxymethylpyrrolidine hydrochloride

A solution of 15 mg (0.078 mmol) of 2-imino-5-(S)-acetyloxymethylpyrrolidine hydrochloride prepared in example 81 in 3 mL of methanol was saturated with NH_3 and the solution was stirred for 3 h. The reaction mixture was concentrated and the residual solid was suspended in Et_2O-EtOAc, filtered and washed with Et_2O and dried to isolate 6 mg of the title compound.

^{1}H NMR (D_2O): 4.10 (m, 1H), 3.70 (m, 1 H), 3.57 (m, 1H), 2.87 (m, 2H), 2.29 (m,1H), 1.97 (m, 1H).

Mass spectrum m/e = 115 (M+1)

EXAMPLE 84



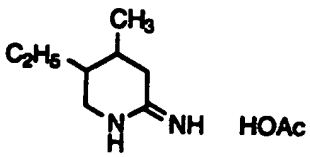
2-Imino-5-(R)-hydroxymethylpyrrolidine hydrochloride

The title compound was obtained from 2-imino-5-(R)-acetyloxymethylpyrrolidine hydrochloride (example) by the method described in example 83.

^{1}H NMR (D_2O): 4.12 (m, 1H), 3.72 (dd, 1 H), 3.57 (dd, 1H), 2.88 (m, 2H), 2.3 (m, 1H), 1.96 (m, 1H).

Mass spectrum m/e = 115 (M+1)

EXAMPLE 85



5-Ethyl-2-imino-4-methyl-piperidine, acetic acid salt

Step A: 5-Nitro-4-methyl-2-trimethylacetylaminopyridine

To a mixture of 5-nitro-4-methyl-2-aminopyridine (1.0 g, 6.53 mmol) in 15 mL of methylene chloride was added triethylamine (1.14 mL, 8.16 mmol) and cooled to 0 °C. To this was added dropwise a solution of trimethylacetyl chloride (0.89 mL, 7.18 mmol) and the mixture allowed to warm to room temperature and stirred 72 h. The solution was diluted with 100 mL of methylene chloride, washed with saturated sodium bicarbonate, water, brine, dried (Na_2SO_4), and evaporated to an amber oil. This was subjected to flash silica gel chromatography using 10% ethyl acetate/hexane as eluant to yield the title compound.

^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (s,9H); 2.65 (s,3H); 8.18 (b,1H); 8.29 (s,1H); 8.94 (s,1H)

Step B: 5-Amino-4-methyl-2-trimethylacetylaminopyridine

A solution of 5-nitro-4-methyl-2-trimethylacetylaminopyridine (4.5 g, 18.97 mmol) in 50 mL of acetic acid containing 10% palladium/carbon was hydrogenated at atmospheric pressure for 48 h. The catalyst was removed by filtration and the filtrate was concentrated. The residue was coevaporated with toluene to give the title compound.

^1H NMR (400MHz, $CDCl_3$): δ 1.29 (s,9H); 2.19 (s,3H); 7.60 (s,1H); 8.04 (s,1H); 8.50 (b,1H)

Step C: 5-Iodo-4-methyl-2-trimethylacetylaminopyridine

A mixture of 5-amino-4-methyl-2-trimethylacetylaminopyridine (1.0 g, 4.82 mmol) in 34 mL of diiodomethane containing isoamyl nitrite (4.0 mL, 29.77 mmol) was heated at 85 °C for 0.5 h, cooled to room temperature and evaporated at 60 °C under high vacuum to give a red semi-solid. The crude material

was subjected to flash chromatography using 10% ether / hexane as eluant to give the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s,9H); 2.40 (s,3H); 7.90 (b,1H); 8.22 (s,1H); 8.45 (s,1H)

Step D: 5-Ethynyl-4-methyl-2-trimethylacetylaminopyridine

To a mixture of 5-iodo-4-methyl-2-trimethylacetylaminopyridine (176 mg, 0.55 mmol) in tetrahydrofuran (0.60 ml), triethyamine (3.32 ml), bis(triphenylphosphine)palladium(II)chloride (4 mg), copper (I) iodide (1.1 mg) and (trimethylsilyl)acetylene (117 ul, 0.83 mmol) were added. The mixture was stirred at room temperature for 3 h. The mixture was diluted with chloroform (50 mL) , dried (Na_2SO_4), and evaporated to give a tan solid. The crude solid was dissolved in methanol (5 mL), treated with 1N potassium hydroxide (0.61 mL) and stirred at room temperature 18 h. The mixture was evaporated to dryness, taken up in chloroform (50 mL), dried (Na_2SO_4), and evaporated to give a solid. The product was purified by flash chromatography using 10% ethyl acetate / hexane to yield the title compound.

^{1}H NMR (400MHz, CD_3OD): δ 1.30 (s,9H); 2.45 (s,3H); 3.85 (s,1H); 8.02 (s,1H); 8.30 (s,1H)

Mass spectrum m/e = 217 (M+1).

Step E: 5-Ethyl-4-methyl-2-trimethylacetylaminopyridine

A solution of 5-ethynyl-4-methyl-2-trimethylacetylaminopyridine (115 mg, 0.53 mmol) in ethyl acetate (2 mL) containing 10% palladium / carbon (20 mg) was hydrogenated at atmospheric pressure for 15 minutes. The catalyst was removed by filtration through a Millex-HV 0.45 um Filter Unit and the filtrate was

concentrated. Purification was achieved by flash chromatography using 10% ethyl acetate / hexane to give the title compound.

^{1}H NMR (400MHz, CD_3OD): δ 1.20 (t,3H); 1.30 (s,9H); 2.34 (s,3H); 2.65 (q,2H); 7.84 (s,1H); 8.02 (s,1H)

Mass spectrum: m/e = 221 (M+1).

Step F: 5-Ethyl-4-methyl-2-aminopyridine

A solution of 5-ethyl-4-methyl-2-trimethylacetylaminopyridine (192 mg, 0.87 mmol) in 2N hydrochloric acid (3 mL) was refluxed at 100° for 18 h. The mixture was diluted with water (10 mL) and washed with ether. The aqueous layer was made basic with 10% sodium carbonate and extracted with ethyl acetate. The EtOAc layer was dried (Na_2SO_4) and evaporated to give the title compound.

^{1}H NMR (400 MHz, CD_3OD): δ 1.14 (t,3H); 2.20 (s,3H); 2.50 (q,2H); 6.42 (s,1H); 7.60 (s,3H)

Mass spectrum: m/e = 136 (M+).

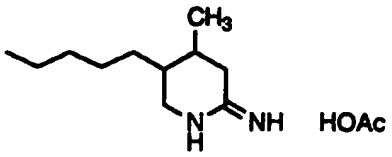
Step G: 5-Ethyl-2-imino-4-methyl-piperidine, acetic acid salt

A solution of 5-ethyl-4-methyl-2-aminopyridine (42 mg, 0.31mmol) in acetic acid (1 mL) containing platinum oxide (25 mg) was hydrogenated at 40 psi for 6 h. The catalyst was removed by filtration through a Millex-HV 0.45um Filter Unit and the filtrate was evaporated to give the title compound.

^{1}H NMR (400MHz, CD_3OD): δ 0.97 (m,6H); 1.35-3.50 (m,5H); 2.63-3.50 (m,3H)

Mass spectrum m/e = 141 (M+1).

EXAMPLE 86



2-Imino-4-methyl-5-(1-pentyl)-piperidine, acetic acid salt

Step A: 5-(1-Pentynyl)-4-methyl-2-trimethylacetylaminopyridine

The above compound was prepared in a similar fashion as Example 85, Step D, but substituting 1-pentyne in place of (trimethylsilyl)acetylene to yield the title compound.

^{1}H NMR (400 MHz, CD_3OD): δ 1.08 (t,3H); 1.30 (s,9H); 1.65 (q,2H); 2.40 (s,3H); 2.45 (t,2H); 7.98 (s,1H); 8.20 (s,1H)

Step B: 5-(1-Pentyl)-4-methyl-2-trimethylacetylaminopyridine

A solution of 5-(1-pentynyl)-4-methyl-2-trimethylacetylaminopyridine (225 mg, 0.87 mmol) in ethyl acetate (4.5 ml) containing platinum oxide (45 mg) was hydrogenated at atmospheric pressure for 1.5 h. The catalyst was removed by filtration through a Millex-HV 0.45um Filter Unit. Evaporation of the filtrate gave the title compound.

^{1}H NMR (400 MHz, CD_3OD): δ 0.95 (t,3H); 1.33(s,9H); 1.40 (m,4H); 1.60 (m,2H); 2.35 (s,3H); 2.63 (m,2H); 7.84 (s,1H); 8.00 (s,1H)

Mass spectrum m/e = 263 (M+1).

Step C: 5-(1-Pentyl)-4-methyl-2-aminopyridine

A suspension of 5-(1-pentyl)-4-methyl-2-trimethylacetylamino-pyridine (233 mg, 0.89 mmol) in 2N hydrochloric acid (3 mL) was heated at 100 °C for 18 h. The solution was cooled to room temperature, made basic with 20% aqueous sodium carbonate and extracted with chloroform. The organic layer was dried (Na_2SO_4), and evaporated. The product was purified by flash chromatography using 2% methanol / methylene chloride to give the title compound.

^1H NMR (400MHz, CD_3OD): δ 0.90 (t,3H); 1.35 (s,4H); 1.50 (m,2H); 2.20 (s,3H); 2.45 (m,2H); 6.40 (s,1H); 7.58 (s,1H)

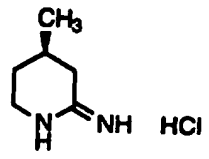
Mass spectrum m/e = 179 (M+1).

Step D: 2-Imino-4-methyl-5-(1-pentyl)-piperidine, acetic acid salt

The above compound was prepared in a similar fashion as Example 85, Step G, but substituting 5-(1-pentyl)-4-methyl-2-aminopyridine in place of 5-ethyl-4-methyl-2-aminopyridine to yield the title compound.

^1H NMR (400MHz, CD_3OD): δ 0.93 (m,6H); 1.50-1.76 (m,4H); 2.10-2.43 (m,4H); 2.65-2.80 (m,2H); 2.95-3.15 (m,2H); 3.35-3.50 (m,2H)
Mass spectrum: m/e = 183 (M+1).

EXAMPLE 87



4(R)-Methyl-2-iminopiperidine hydrochloride

Step A: Methyl (R)-citronellate

Diazomethane in ether was cautiously added to a solution of (R)-citronellic acid (17.2 g, 0.1 M) in ether at 0° C until yellow color persisted. After the addition was complete, the reaction mixture was stirred 30 mins and the solvent was removed in vacuo to give the quantitative yield of the desired methyl ester as a colorless oil.

^{1}H NMR ($CDCl_3$): 0.92(d,3H); 1.2(m,1H); 1.32(m,1H); 1.58(s,3H); 1.65(s,3H); 1.95(m,2H); 2.1(q,1H); 2.4(q,1H); 3.64(s,3H); 5.06(t,1H)

Step B: Methyl 3(R)-methyl-5-hydroxycarbonylpentanoate

A stream of 4% ozone in oxygen was passed through a solution of methyl (R)-citronellate (7 g, 39 mmol) in 140 mL of glacial acetic acid at room temperature for 45 mins. 14 mL of 30% hydrogen peroxide was then added and the reaction mixture was heated to reflux 2 hrs. Solvent was removed in vacuo to afford 6.5 g of the desired acid as a colorless oil.

^{1}H NMR ($CDCl_3$): 0.94(d,3H); 1.52(m,1H); 1.69(m,1H); 1.98(m,1H); 2.15(q,1H); 2.3(q,1H); 2.36(m,2H)

Step C: Methyl 3(R)-methyl-5-benzyloxycarbonylamino pentanoate

Diphenyl phosphoryl azide (5.3 mL, 24.53 mmol) was added to a mixture of methyl 3(R)-methyl-5-hydroxycarbonyl pentanoate (3.88 g, 22.3 mmol) and triethylamine (3.45 mL, 24.53 mmol) in 22 mL of p-xylene. The mixture was then stirred 1 hr at 80° C. 4.5 mL (45 mmol) of benzyl alcohol was then added and the mixture was heated at reflux for 4 hr. The reaction miture was cooled, diluted with ethyl acetate and washed with water, and sodium chloride and dried over ahydrous magnesium sulfate. Solvent removal gave a crude product, which was

purified on silica gel using 10% ethyl acetate in hexane as solvent to afford 3.9 g of the desired carbamate as an oil.

^{1}H NMR ($CDCl_3$): 0.95(d,3H); 1.4(m,1H); 1.62(m,1H); 2.02(m,1H); 2.18(q,1H); 2.3(q,1H); 3.22(m,2H); 3.65(s,3H); 5.07(s,2H); 7.3(m,5H)

Step D: 3(R)-Methyl-5-benzyloxycarbonylamino pentanoic acid

A 2N sodium hydroxide (7.5 ml, 15 mmol) solution was added to 3.9 g (14 mmol) of methyl 3R-methyl-5-benzyloxycarbonylamino pentanoate in 70 mL of 2:1 mixture of methanol:water. This mixture was then heated 1 hr at 60° C and 7.5 mL of 2N hydrochloric acid was added after cooling. Most of the volatiles were removed in vacuo. The remaining mixture was extracted with ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous magnesium sulfate. Solvent removal afforded 2.9 g of the desired acid as an oil.

^{1}H NMR ($CDCl_3$): 0.98 (d,3H); 1.42(m,1H); 1.56(m,1H); 2.02(m,1H); 2.2(m,1H); 2.35(m,1H); 3.2(m,2H); 5.08(s,2H); 7.3(m,5H)

Step E: 4(R)-Methyl-1-benzyloxycarbonyl-2-piperidone

Ethyl chloroformate (1.92 mL, 20 mmol) was added dropwise to a solution of 3(R)-methyl-5-benzyloxycarbonylamino pentanoic acid (2.65 g, 10 mmol) and triethyl amine (2.8 mL, 20 mmol) in 50 mL of ethyl acetate at 0° C. After stirring 1 hr at room temperature, the solids formed were filtered and washed with ethyl acetate. The filtrate was concentrated to give an oil which was taken up in 45 mL of toluene. This solution was heated to reflux for 4 hr. Solvent was then removed in vacuo and the residue was purified on silica gel using 20% ethyl acetate in hexane as solvent to give 1.39 g of the desired lactam as an oil.

^{1}H NMR ($CDCl_3$): 1.02(d,3H); 1.44(m,1H); 2.0(m,3H); 3.62(q,1H); 3.55(q,1H); 3.88(q,1H); 5.28(2H); 7.35(m,5H)

Step F: 4(R)-Methyl-2-piperidone

10% Palladium hydroxide on carbon (350 mg) was added to a solution of 4(R)-Methyl-1-benzyloxycarbonyl-2-piperidone (1.3 g) in 20 mL of methanol and the mixture was hydrogenated on Parr shaker at 50 psi and room temperature. After 4 hrs, the catalyst was filtered and washed with methanol. The filtrate was concentrated to give 700 mg of the crude product which was purified on silica gel using 5% methanol in ethyl acetate as solvent to give 510 mg of the desired lactam as a white solid.

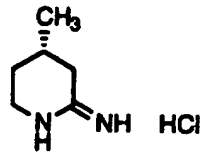
^{1}H NMR (DMSO): 0.92 (d,3H); 1.26 (m,1H); 1.75(m,3H); 2.18(q,1H); 3.12 (m,2H)

Step G: 4(R)-Methyl-2-imino piperidine hydrochloride

The title compound was prepared from 4R-methyl-2-piperidone as described in Examples 2 and 3.

^{1}H NMR (DMSO): 0.96(d,3H); 1.25(m,1H); 1.75(m,1H); 1.85(m,1H); 2.15(q,1H); 2.55(q,1H0; 3.24(m,1H); 3.34(m,1H); 8.28(b,1H); 8.62(b,1H); 9.35(b,1H)

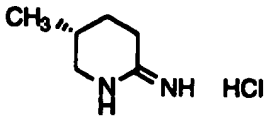
EXAMPLE 88



4(S)-Methyl-2-iminopiperidine hydrochloride

The title compound was synthesized according to the procedure of Example 87 starting with (S)-citronellic acid.

EXAMPLE 89



5(R)-Methyl-2-iminopiperidine hydrochloride

Step A: 2(R),6-Dimethyl-1-benzyloxycarbonylamino-5-heptene

Diphenylphosphoryl azide (14 mL, 65 mmol) was added dropwise to a solution of (R)-citronellic acid (10g, 59 mmol) and triethylamine (9.1 mL, 65mmol) in 60 mL of toluene. The mixture was heated for 1 hr at 80° C. 12 mL (120 mmol) of benzyl alcohol was added and the mixture was heated to reflux for 4 hrs. The reaction mixture was cooled, diluted with ethyl acetate and washed with water, saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvent was removed in vacuo to give a crude product which was purified on silica gel using 5% ethyl acetate in hexane as solvent to afford 9.8 g of the desired carbamate as a thick oil.

^{1}H NMR ($CDCl_3$): 0.89(d,3H); 1.13(m,1H); 1.35(m,1H); 1.5(m,1H); 1.6(m,1H); 1.58(s,3H); 1.66(s,3H); 1.98(m,1H); 3.0(m,1H); 3.14(m,1H); 5.06(m,1H); 5.08(s,2H); 7.35(m,5H)

Step B: 5(R)-Methyl-1-benzyloxycarbonyl-2-piperidone

Ozone in oxygen (4%) was passed through a solution of 2-(R),6-dimethyl-1-benzyloxycarbonylamino-5-heptene (9.8 g) in 150 mL of methylene chloride at -78° C until the blue color persisted. Nitrogen

was then bubbled for 15 mins. 16 mL of dimethyl sulfide was added and the mixture was stirred 1 hr as it warmed to room temperature and then concentrated to give a residual oil. This was taken up in 100 mL of acetone and cooled in ice bath. Jones reagent was added dropwise until orange color was sustained. After stirring 30 mis, 4 mL of isoprpopyl alcohol was added and the mixture was stirred for an additional 15 mins. Solvent was then removed in vacuo and the residue was stirred with water and ethyl acetate. The organic phase was separated and the aqueous phase was extracted with ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous magnesium sulfate and the solvent was removed in vacuo. The resulting residue was purified on silica gel using first 10% ethyl acetate in hexane as solvent to give 2.0 g of 5(R)-methyl-1-benzyloxycarbonyl-2-piperidone as an oil.

^{1}H NMR ($CDCl_3$): 1.02(d,3H); 1.45(m,1H); 1.87(m,1H); 1.94(m,1H); 2.54(m,2H); 3.16(q,1H); 3.88(q,1H); 5.26(s,2H); 7.36(m,5H)

Further elution of the column with 1% methanol in ethyl acetate gave 5.8 g of 3(R)-methyl-N-(benzyloxycarbonyl)-N-formyl-4-aminobutanoic acid as a thick oil, which can be utilized in the synthesis of 4-(R)-2-imino-4-methylpyrrolidne.

Step C: 5(R)-Methyl-2-piperidone

10% Palladium hydroxide on carbon (700 mg) was added to a solution of 4(R)-methyl-1-benzyloxycarbonyl-2-piperidone (2.0 g) in 40 mL of methanol and the mixture was hydrogenated on Parr shaker at 50 psi and room temperature. After 4 hrs, the catalyst was filtered and washed with methanol. The filtrate was concentrated to give 1.4 g of the crude product, which was purified on silica gel using 5% methanol in ethyl acetate as solvent to give 1 g of the desired lactam as a white solid.

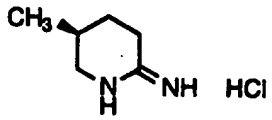
^{1}H NMR ($CDCl_3$): 1.0(d,3H); 1.45(m,1H); 2.86(m,2H); 2.38(m,2H); 2.9(q,1H); 3.3(q,1H)6.6(b,1H)

Step D: 5(R)-Methyl-2-iminopiperidine hydrochloride

The title compound was synthesized from 5(R)-methyl-2-piperidone according to the procedure described in Examples 2 and 3.

^{1}H NMR (DMSO): 0.93(d,3H); 1.34(m,1H); 1.76(m,2H); 2.54(q,2H); 2.8(q,1H); 3.32(m,1H); 8.35(b,1H); 8.68(b,1H); 9.42(b,1H).

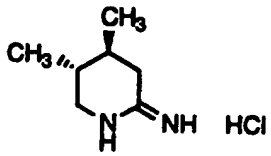
EXAMPLE 90



5(S)-Methyl-2-iminopiperidine hydrochloride

The title compound was prepared by the method of example 89 starting with (S)-citronellic acid.

EXAMPLE 91



4(S),5(R)-Dimethyl-2-imino-piperidine hydrochloride:

Step A:(S)-Citronelloyl chloride

Oxalyl chloride (8.1 mL, 92 mmol) of was added to 14.4 g (83.75 mmol) of (S)-Citronellic acid in 150 mL of methylene chloride at

0 °C. 12.9 mL (92 mmol) of triethylamine was then added dropwise cautiously so that the gases evolved can be vented effectively. After the addition was complete, the mixture was stirred 1 hour at the same temperature. After dilution with 300 mL of ether, the solids precipitated were filtered and washed with ether. The filtrate was concentrated to give a brown liquid. This was dissolved in ether and the small amount of solid was filtered and washed with ether. The filtrate was concentrated in vacuo to give almost quantitative yield of the desired acid chloride as brown oil.

^{1}H NMR ($CDCl_3$): 1.0(d, 3H); 1.58(s,3H); 1.68(s,3H); 2.66 & 2.88(2q; 2H); 5.05(t,1H)

Step B: 3(3(S),7-Dimethyl-6-octenoyl)-4(R)-phenylmethyl-2-oxazolidinone

A 1.6M solution of n-butyllithium (52 mL, 83 mmol) was added dropwise to a solution of 4R-phenylmethyl-2-oxazolidinone (13.3g, 75 mmol) in 150 mL of THF at -78 °C. The reaction mixture was stirred for 15 min after the addition and a solution of the above S-citronelloyl chloride in 50 mL of THF was added dropwise and the mixture was stirred for 15 min at that temperature. The cooling bath was removed and the mixture was allowed to warm to room tempoerature and stirred 1 hr at room temperature. After quenching with saturated ammonium chloride solution, the reaction mixture was partitioned between 1N hydrochloric acid and ethyl acetate. The ethyl acetate extracts were washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Solvent removal gave an oil which was chromatographed on silica gel using 10% ethyl acetate in hexane as solvent to give the title compound in 65% yield.

^{1}H NMR ($CDCl_3$): 1.0(d,3H); 1.6(s,3H); 1.66(s,3H); 2.74(q,1H); 2.85(m;2H); 3.3(q,1H); 4.15(m,2H); 4.66(m,1H); 5.08(t,1H); 7.28(m,5H)

Step C: 3(2(R),3(S),7-Trimethyl-6-octenoyl)-4(R)-phenylmethyl-2-oxazolidinone

55 mL (55 mmol) of 1M solution of sodium bis(trimethylsilyl)amide in THF was added dropwise to a solution of 15 g (45.4 mmol) of 3(3(S),7-dimethyl-6-octenoyl)-4(R)-phenylmethyl-2-oxazolidinone in 120 mL of THF at -78 °C. The reaction mixture was stirred 30 mins at that temperature and 21 mL (333 mmol) of methyl iodide in 20 mL of THF was added dropwise. The resulting mixture was stirred 1 day at -78 °C. After warming to room temperature, the reacton mixture was quenched with ammonium chloride solution and partitioned between 1N hydrochloric acid and ethyl acetate. The ethyl acetate extracts were washed with sodium thiosulfate solution, saturated sodium bicarbonate solution, brine and dried over anhydrous magnesium sulfate. Solvent removal afforded essentailly pure desired methylated oxazolidinone derivative in quantitative yield.

^{1}H NMR ($CDCl_3$): 0.88(d, 2H); 1.13(d,3H); 1.58(s,3H); 1.66(s,3H); 2.75(q,1H); 3.26(q,1H); 3.68(m,1H); 4.15(m,2H); 4.63(m,1H); 5.08(t,1H)7.25(m,5H)

Step D: 2(R),3(S),7-Trimethyl-6-octen-1-ol

A solution of 6.8 g (20 mmol) of 3(2(R),3(S),7-trimethyl-6-octenoyl)-4(R)-phenylmethyl-2-oxazolidinone in 30 mL of THF was added dropwise to a suspension of 1.634 g (43 mmol) of lithium aluminum hydride in 40 mL of THF at 0 °C. The reaction mixture was then stirred 6 h at ambient temperature The reaction mixture was then recooled in ice bath and 5 mL of methanol was added dropwise very cautiously. After the effervescence subsided, the reaction mixture was concentrated to about 30% of the original volume The reaction mixture was then stirred with saturated solution of potassium sodium tartrate and extracted with ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous magnesium sulfate. Solvent removal afforded a

crude oil, which was purified on silica gel using 10% ethyl acetate in hexane as solvent to give 2.0 g (62%) of the desired alcohol as a colorless oil.

^{1}H NMR ($CDCl_3$): 0.78(d, 2H); 0.79(d,2H);1.6(s,3H); 1.66(s,3H); 3.44(q,1H); 3.54(q,1H); 5.1(t,1H)

Step E: 2(R),3(S),7-Trimethyl-6-octen-1-methanesulfonate

To a solution of 510 mg (3 mmol) of 2(R),3(S),7-trimethyl-6-octen-1-ol in 3 mL of pyridine at ice bath temperature 0.7 mL (9 mmol) of methanesulfonyl chloride was dropwise added. The mixture was then stirred for 8 hrs at room temperature. After diluting with ethyl acetate, the reaction mixture was washed with saturated sodium bicarbonate, 1N citric acid and water. After drying over anhydrous magnesium sulfate, the solvent was removed to give 722 mg of the desired mesylate as a yellow oil.

^{1}H NMR ($CDCl_3$): 0.8(d,3H); 0.87(d,3H); 1.6(s,3H); 1.67(s,3H); 2.98(s,3H); 4.02(q,1H); 4.13(q,1H); 5.06(t,1H)

Step F: 2(R),3(S),7-Trimethyl-1-azido-6-octene

975 mg (15 mmol) of sodium azide was added to a solution of 2(R),3(S),7-trimethyl-6-octen-1-methane sulfonate (720 mg, ~3 mmol) in 6 mL of N,N-dimethylformamide and the mixture was heated overnight at 80° C. The reaction mixture was diluted with ethyl acetate and washed several times with saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvents were removed in vacuo to give crude azide as an oil. This material was purified on silica gel using 30% ether in hexane as solvent to give 545 mg of the desired azide as a colorless oil.

^{1}H NMR ($CDCl_3$): 0.78(d,3H); 0.84(d,3H); 1.59(s,3H); 1.66(s,3H); 3.1(q,1H); 3.21(q,3H); 5.07(t,1H)

Step G: 2(R),3(S),7-Trimethyl-1-amino-6-octene

6.3 mL (6.3 mmol) of 1M lithium aluminum hydride in THF was added dropwise to a solution of 2(R),3(S),7-trimethyl-1-azido-6-octene in 10 mL of THF at 0° C. The reaction mixture was heated to reflux 18 hrs. After cooling in ice bath, ~ 1 mL of methanol was added dropwise cautiously. After the effervescence stopped, the reaction mixture was concentrated to 30% of the volume and 1N solution of potassium sodium tartrate was added. After stirring 15 mins, the reaction mixture was extracted with ethyl acetate. The combined ethyl acetate layers were dried over anhydrous magnesium sulfate and the solvent was removed to give 399 mg of the desired amine as an oil.

^{1}H NMR ($CDCl_3$): 0.76(d,3H); 0.78(d,3H); 1.60(s,3H); 1.67(s,3H); 2.49(q.1H); 2.62(q,1H); 5.1(t,1H)

Step H: 2(R),3(S),7-Trimethyl-1-benzyloxycarbonylamino-6-octene

Separate solutions of 2(R),3(S),7-trimethyl-1-amino-6-octene (0.87 g, 5.2 mmol) in 8 mL of dioxane, and benzyl chloroformate (0.86 mL, ~6 mmol) in 8 mL of dioxane were added dropwise simultaneously to a stirred solution of 1.05 g (10.5 mmol) of potassium hydrogen carbonate in 20 mL of water at 0° C. After the additions, the mixture was stirred 8 hrs at room temperature. Most of the volatile solvents were removed in vacuo. The remaining reaction mixture was extracted with ethyl acetate. The combined organic phases were dried over anhydrous magnesium sulfate. Solvent removal gave the crude product which was purified on silica gel using 10% ethyl acetate in hexane as solvent to give 1.4 g of the desired carbamate as a colorless oil.

^{1}H NMR ($CDCl_3$): 0.77(d,6H); 1.18(m,1H); 1.3(m,1H); 1.5(m,1H); 1.6(s,3H); 1.66(s,3H); 1.95(m,2H); 3.04(m,1H); 1.12(m,1H); 4.7(b,1H); 5.08(s & m,3H)7.34(m,5H)

Step I: 4(S),5(R)-Dimethyl-6-benzyloxycarbonylamino-hexan-1-al

A stream of 4% ozone in oxygen was bubbled through a solution of 1.79 g (~6 mmol) of 2(R),3(S),7-trimethyl-1-benzyloxycarbonylamino-6-octene in 25 mL of methylene chloride at -78° C until blue color persisted. Nitrogen gas was bubbled through the reaction mixture at the same temperature for 15 min. 3 mL of dimethyl sulfide was added and the mixture was stirred 15 mins and then warmed to 0° C. The solvents and other volatile materials were removed under house vacuum. Traces of solvent were then removed in vacuo to give 1.3 g of the desired aldehyde as a thick oil.

^{1}H NMR ($CDCl_3$): 0.8(2d,6H); 1.48 & 1.54(m,4H); 2.42(m,2H); 3.04(m,1H); 3.14(m,1H); 5.08(s,2H); 7.34(m,5H); 9.74(s,1H)

Step J: 3(R),4(S)-Dimethyl-1-benzyloxycarbonyl-2,3,4,5-tetrahydro-azepine

A mixture of 1.2 g (~4.2 mmol) of 4(S),5(R)-dimethyl-6-benzyloxycarbonylamino-hexan-1-al, 1.26 mL (13.2 mmol) of acetic anhydride and 120 mg (1.2 mmol) of potassium acetate was heated at 160 °C for 2 hours . Excess acetic anhydride was removed in vacuo and the residue was purified on silica gel using 20% ethyl acetate in hexane as solvent to give ~190 mg of the desired azepine derivative as an oil.

^{1}H NMR ($CDCl_3$): 0.95 & 1.0 (2d,6H); 2.0(m,1H); 2.17(m,1H); 3.64(m,1H); 3.74(m,1H); 4.9(m,1H); 5.1(s,2H); 6.6(m,1H); 7.35(m.1H)

Step K: 3(S),4(R)-Dimethyl-6-(benzyloxycarbonyl)formimido-1-pentanoic acid

A stream of 4% ozone in oxygen was bubbled through a solution of 130 mg (0.5 mmol) of 3(R),4(S)-dimethyl-1-benzyloxycarbonyl-2,3,4,5-tetrahydroazepine in 5 mL of glacial acetic acid at room temperature for 10 mins. 0.3 mL of 30% hydrogen peroxide was added and the mixture was heated to reflux 2 hrs. The solvent was removed and the traces were azeotroped with toluene to give 100 mg of the desired acid as a thick oil.

^{1}H NMR ($CDCl_3$): 0.76(d,3H); 0.87(d,3H); 1.9(m,1H); 2.0(m,1H); 2.18(q,1H); 2.32(q,1H); 3.5(q,1H); 3.6(q,1H); 5.28(s,2H); 7.37(m,5H); 9.26(s,1H)

Step L: 3(S),4(R)-Dimethyl-6-benzyloxycarbonylamino-1-pentanoic acid

A solution of 2N sodium hydroxide (0.4 mL, 0.8 mmol) was added to a solution of 90 mg (0.3 mmol) of 3(S),4(R)-dimethyl-6-(benzyloxycarbonyl)formamido-1-pentanoic acid in a mixture of 2 mL of methanol and 1 mL of water. This mixture was heated 2 hrs at 60° C. The reaction mixture was cooled and 0.4 mL of 2N hydrochloric acid was added. Solvents were removed and the residue was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and the solvent removal afforded 62 mg of the desired acid as an oil.

^{1}H NMR ($CDCl_3$): 0.82(d,3H); 0.88(d,3H); 1.68(m,1H); 2.08(m,1H); 2.2(m.1H); 2.35(m,1H); 3.1(m,2H); 5.1(2H); 7.3(m,5H)

Step M: 4(S),5(R)-Dimethyl-2-piperidone

Ethyl chloroformate (0.048 mL, 0.5 mmol) was added to a solution of 3(S),4(R)-dimethyl-6-benzyloxycarbonylamino-1-pentanoic acid (62 mg, 0.25 mmol) and triethylamine (0.07 mL, 0.5 mmol) in 2 mL of ethyl acetate cooled in ice bath. After stirring 1 hr, the solids were

filtered and washed with ethyl acetate. The filtrate was concentrated to give the carbonate as oil. 2 mL of toluene was added to this resiue and heated to reflux 5 hrs. The solvent was then removed in vacuo to give the N-protected lactam as oil. 25 mg of palladium hydroxide was added to a solution of the above residue in 2 mL of methanol and the mixture was hydrogenated 4 hrs on a Parr shaker. The catalyst was filtered and washed with methanol. The filtrate was concentrated to give 31 mg of the desired lactam as a waxy solid.

^{1}H NMR ($CDCl_3$): 0.95(d,3H); 0.97(d,3H); 1.54(m,2H); 1.98(m,1H); 2.44(m,1H); 2.9(m,1H); 3.25(m,1H).

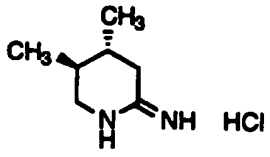
Step N: 4(S),5(R)-Dimethyl-2-iminopiperidine hydrochloride

The title compound was prepared from 4(S),5(R)-Dimethyl-2-piperidone according to the procedure described in examples 2 and 3.

^{1}H NMR (DMSO): 0.89(d,3H); 0.93(d,3H); 1.50(m,2H); 2.20(m,1H); 2.55(m,1H); 2.83(m,1H); 8.3(b,1H); 8.65(b,1H); 9.40(b,1H)

Specific rotation = +62.8° (c=0.21, EtOH)

EXAMPLE 92

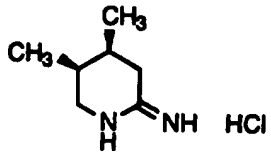


4(R),5(S)-Dimethyl-2-imino-piperidine hydrochloride:

The title compound is prepared according to the procedure of Example 89 starting with (R)-citronellic acid and 4(S)-phenylmethyl-2-oxazolidinone.

Specific rotation = -65.2° (c=0.21, EtOH)

EXAMPLE 93



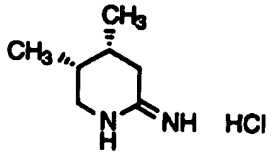
4(S),5(S)-Dimethyl-2-imino-piperidine hydrochloride:

The title compound is prepared according to the procedure of Example 91 starting with (S)-citronellic acid and 4(S)-phenylmethyl-2-oxazolidinone.

^{1}H NMR (DMSO): 0.84(d,3H); 0.86(d,3H); 1.98(m,1H); 2.26(m,1H); 2.64(m,1H); 2.98(m,1H); 7.25(b,1H); 8.25(b,1H); 8.64(b,1H)

Specific rotation = -23° (c=0.2, EtOH)

EXAMPLE 94

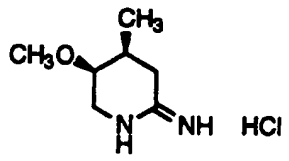


4(R),5(R)-Dimethyl-2-imino-piperidine hydrochloride:

The title compound is prepared according to the procedure of Example 91 starting with (R)-citronellic acid and 4(R)-phenylmethyl-2-oxazolidinone.

Specific rotation = +25° (c=0.22, EtOH)

EXAMPLE 95



2-Imino-5(S)-methoxy-4(S)-methyl-piperidine hydrochloride.

Step A: 5-O-*tert*-Butyldimethylsilyl-2,3-dideoxy-D-*glycero*-pent-2-eno-1,4-lactone

To a solution of 2,3-dideoxy-D-*glycero*-pent-2-eno-1,4-lactone (580 mg, 5.08 mmol) in dry N,N-dimethylformamide (DMF) (7 mL) were added triethylamine (1.06 mL, 7.60 mmol) and 4-dimethylaminopyridine (63 mg, 0.51 mmol). The reaction mixture was cooled in an ice-bath, and *tert*-butyldimethylsilyl chloride (1.02 g, 6.77 mmol) was added. The mixture was allowed to attain room temperature and stirred an additional 3 hours. The mixture was then diluted with diethyl ether, washed with water, 2N hydrochloric acid, saturated sodium bicarbonate solution, saturated brine solution, dried (Na_2SO_4), and evaporated. This procedure was repeated with 600 mg (5.26 mmol) of 2,3-dideoxy-D-*glycero*-pent-2-eno-1,4-lactone. The two runs were combined after workup, and the product was purified by flash chromatography eluting with 15% acetone in hexane. The resulting oil crystallized upon standing; yield 1.65 g (70%).

^1H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.05 (s, 3H), 0.85 (s, 9H), 3.78 (dd, 1H), 3.91 (dd, 1H), 5.03 (m, 1H), 6.14 (dd, 1H), 7.48 (dd, 1H).

Step B: 2,3-Dideoxy-3-C-methyl-5-O-*tert*-butyldimethylsilyl-D-*erythro*-pentono-1,4-lactone

To a vigorously stirred suspension of copper(I) bromide-dimethyl sulfide complex (7.42 g, 36.1 mmol) in diethyl ether (80 mL) was added methyllithium (51 mL of a 1.4M solution in hexane, 71.4 mmol) over 5-6 minutes. The resulting solution was cooled to -23°C (CCl_4/dry ice bath), and a solution of 5-O-*tert*-butyldimethylsilyl-2,3-dideoxy-D-*glycero*-pent-2-eno-1,4-lactone (1.65 g, 7.22 mmol) was added in one portion. The suspension was stirred at -23°C for 20 minutes and quenched by the cautious addition of saturated aqueous ammonium chloride (39 mL). The mixture was transferred to a separatory funnel and shaken vigorously to break down excess reagent. The organic layer was washed with saturated brine solution, dried ($MgSO_4$), and evaporated. The product was purified by flash silica gel chromatography eluting initially with 5% ethyl acetate in hexane and subsequently with 10% ethyl acetate in hexane; yield 1.42 g (80%).

^1H NMR (400 MHz, $CDCl_3$): δ 0.04 (s,3H), 0.06 (s, 3H), 0.88 (s, 9H), 1.16 (d, 3H), 2.11 (dd, 1H), 2.52 (m, 1H), 2.77 (m, 1H), 3.71 (dd, 1H), 3.82 (dd, 1H), 4.08 (m, 1H).

Step C: 2,3-Dideoxy-3-C-methyl-D-*erythro*-pentono-1,4-lactone

2,3-Dideoxy-3-C-methyl-5-O-*tert*-butyldimethylsilyl-D-*erythro*-pentono-1,4-lactone (1.4 g, 6.13 mmol) was treated with tetra-n-butylammonium fluoride (8.7 mL of a 1.0M solution in tetrahydrofuran, 8.7 mmol) for 90 minutes at room temperature. The reaction mixture was evaporated, and the crude product subjected to flash silica gel chromatography eluting initially with 15% acetone in hexane and subsequently with 25% acetone in hexane. Pure title compound was obtained as an oil; yield 710 mg (89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (d, 3H), 2.21 (dd, 1H), 2.50 (m, 1H), 2.72 (dd, 1H).

STEP D: 5-Azido-2,3,5-trideoxy-3-C-methyl-D-*erythro*-pentono-1,4-lactone

To a solution of 2,3-dideoxy-3-C-methyl-D-*erythro*-pentono-1,4-lactone (490 mg, 3.76 mmol) in methylene chloride (10 mL) cooled in an ice-bath were added 2,6-lutidine (501 mL, 4.30 mmol) and trifluoromethanesulfonic anhydride (682 mL, 4.05 mmol). The reaction mixture was stirred at 0°C for 30 minutes, diluted with methylene chloride, washed with water, 2N hydrochloric acid, saturated sodium hydrogen carbonate solution, saturated brine solution, dried (Na_2SO_4), and evaporated. The crude product was taken up in DMF (6 mL) and treated with sodium azide (856 mg, 13.2 mmol) at room temperature for 30 minutes. The mixture was diluted with ethyl acetate, washed with water, dried (Na_2SO_4), and evaporated. The pure title compound was obtained after flash chromatography eluting with 25% ethyl acetate in hexane; yield 358 mg (61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (d, 3H), 2.21 (dd, 1H), 2.42 (m, 1H), 2.74 (dd, 1H), 3.44 (dd, 1H), 3.60 (dd, 1H), 4.15 (m, 1H); mass spectrum: 128 (M+1 - N_2).

STEP E: 5(S)-Hydroxy-4(S)-methyl-2-piperidone

A solution of 5-azido-2,3,5-trideoxy-3-C-methyl-D-*erythro*-pentono-1,4-lactone (358 mg, 2.31 mmol) in methanol (4 mL) was hydrogenated under a balloon atmosphere of hydrogen gas in the presence of 10% palladium-on-charcoal (50 mg) overnight at room temperature. The catalyst was then removed by filtration through Celite, and the filter washed with methanol. The combined filtrate and washings were evaporated, and the resulting product crystallized upon standing; yield 128 mg (43%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (d, 3H), 2.05 (m, 1H), 2.17-2.28 (m, 2H), 3.27 (dd, 1H), 3.40 (dd, 1H), 3.86 (m, 1H); mass spectrum: 130 (M+1).

STEP F: 2-Imino-5(S)-methoxy-4(S)-methyl-piperidine hydrochloride.

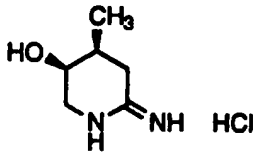
To a solution of 5(S)-hydroxy-4(S)-methyl-2-piperidone (119 mg, 0.921 mmol) in methylene chloride (3 mL) was added trimethyloxonium tetrafluoroborate (285 mg, 1.93 mmol). The reaction mixture was stirred for 24 hours at room temperature. Thin-layer chromatography (10% MeOH/CH_2Cl_2) indicated the formation of two more mobile products: the 5-methoxy-4-methyl imino-methyl ether and the 5-hydroxy-4-methyl imino-methyl ether. The mixture was diluted with ethyl acetate, washed with saturated sodium hydrogen carbonate solution, saturated brine solution, dried ($MgSO_4$), and carefully evaporated (bath temperature <15°C) to avoid loss of the volatile imino ethers. The crude product mixture in ethyl acetate was applied to a column of silica gel (packed as a slurry in 4% methanol/CH_2Cl_2). Rapid elution with 4% methanol/CH_2Cl_2 afforded the 5-methoxy-4-methyl imino-methyl ether (yield ~ 16.7 mg), and subsequent elution with 10% MeOH/CH_2Cl_2 afforded the 5-hydroxy-4-methyl imino-methyl ether (yield ~13.6 mg). Evaporations of the column fractions containing product was performed with extreme caution to avoid loss of the volatile imino ethers.

The 5-methoxy-4-methyl imino-methyl ether (~16.7 mg) was treated with ammonium chloride (4.5 mg) for 4 h in refluxing EtOH (2 mL). The reaction mixture was evaporated, and the resulting solid dried *in vacuo*; yield 14.3 mg.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (d, 3H), 2.12 (m, 1H), 2.40 (dd, 1H), 2.53 (dd, 1H), 3.40 (s, 3H), 3.52 (m, 1H), 3.67 (dd, 1H).

Mass spectrum m/e = 143 (M+1).

EXAMPLE 96



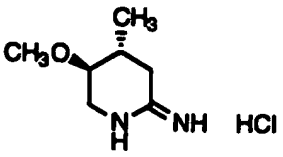
2-Imino-5(S)-hydroxy-4(S)-methyl-piperidine hydrochloride.

The 5-hydroxy-4-methyl-imino methyl ether from Step F of Example 95 (~13.6 mg) was treated with ammonium chloride (4.4 mg) in refluxing EtOH (2 mL) for 4 h . The reaction mixture was evaporated, and resulting solid dried *in vacuo*; yield 9.5 mg.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (d, 3H), 2.08 (m, 1H) ,2.47 (dd, 1H), 2.55 (dd, 1H), 3.40 (dd, 1H), 3.50 (dd, 1H), 3.93 (m, 1H).

Mass spectrum m/e = 129 (M+1).

EXAMPLE 97



2-Imino-5(S)-methoxy-4(R)-methyl-piperidine hydrochloride

Step A: 2,3-Dideoxy-3-C-methyl-5-O-tert-butyldimethylsilyl-D-*threo*-pentono-1,4-lactone

The title compound was prepared according to the method described by S. Hanessian and P.J. Murray for the corresponding 5-O-tert-butyldiphenylsilyl derivative [*Tetrahedron*: 43, 5055-5072, 1987].

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04 (s, 3H); 0.05 (s, 3H); 0.87 (s, 9H); 1.17 (d, 3H); 2.37 (dd, 1H); 2.48 (dd, 1H); 2.71 (m, 1H); 3.78 (dd, 1H); 3.83 (dd, 1H); 4.40 (m, 1H).

Step B: 2,3-Dideoxy-3-C-methyl-D-*threo*-pentono-1,4-lactone

2,3-Dideoxy-3-C-methyl-5-O-tert-butyldimethylsilyl-D-*threo*-pentono-1,4-lactone (1.8 g, 7.36 mmol) was treated with tetra-n-butylammonium fluoride (9.8 mL of a 1.0 M solution in tetrahydrofuran, 9.8 mmol) for 90 minutes at room temperature. The reaction mixture was evaporated, and the crude product subjected to flash chromatography eluting with 25% acetone/hexane; yield 795 mg (83%) of a colorless oil.

Step C: 5-Azido-2,3,5-trideoxy-3-C-methyl-D-*threo*-pentono-1,4-lactone

This compound was prepared in a similar manner as Step D of Example 95 starting with 2,3-dideoxy-3-C-methyl-D-*threo*-pentono-1,4-lactone (795 mg, 6.11 mmol). The title compound was obtained as an oil after flash chromatography eluting with 25% ethyl acetate in hexane; yield 575 mg (61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (d, 3H); 2.31 (dd, 1H); 2.66 (dd, 1H); 3.50 (dd, 1H); 3.57 (dd, 1H); 4.54 (dd, 1H).

Step D: 5(S)-Hydroxy-4(R)-methyl-2-piperidone

A solution of 5-azido-2,3,5-trideoxy-3-C-methyl-D-*threo*-pentono-1,4-lactone (361 mg, 2.33 mmol) in ethyl acetate (23 mL) was hydrogenated at 40 psi in the presence of 20% palladium hydroxide on

carbon (42 mg) for 2 hours at room temperature. The catalyst was removed by filtration through a pad of Celite. The filtrate was evaporated, and the residue taken up in toluene (25 mL) and methanol (2 mL) and heated for 24 hours at 100°C. The mixture was evaporated, and the crude product recrystallized from hot ethyl acetate; yield 160 mg (53%).

^{1}H NMR (400 MHz, CD_3OD): δ 1.04 (d, 3H); 1.95 (m, 1H); 1.99 (dd, 1H); 2.53 (dd, 1H); 3.08 (dd, 1H); 3.41 (dd, 1H); 3.60 (m, 1H).

Step E: 2-Imino-5(S)-methoxy-4(R)-methyl-piperidine hydrochloride

To a solution of 5(S)-hydroxy-4(R)-methyl-2-piperidone (157 mg, 1.22 mmol) in methylene chloride (4 mL) was added trimethyloxonium tetrafluoroborate (376 mg, 2.54 mmol). The reaction mixture was stirred for 24 hours at room temperature. Thin-layer chromatography (10% methanol/CH_2Cl_2) indicated the formation of two more mobile products: the predominant product being the 5-methoxy-4-methyl-imino-methyl ether followed by a smaller amount of the 5-hydroxy-4-methyl-imino-methyl ether. The mixture was diluted with ethyl acetate, washed with saturated sodium hydrogencarbonate solution, saturated brine solution, dried ($MgSO_4$), and carefully evaporated (bath temperature <15°C) to avoid loss of the volatile imino ethers. The crude product mixture was subjected to flash silica gel chromatography (packed as a slurry in 4% methanol/CH_2Cl_2). Rapid elution with 4% methanol/CH_2Cl_2 afforded the 5-methoxy-4-methyl-imino-methyl ether. Subsequent elution with 10% methanol/CH_2Cl_2 afforded the 5-hydroxy-4-methyl-imino-methyl ether. Evaporations of the column fractions containing product were performed with extreme caution to avoid loss of the volatile imino ethers.

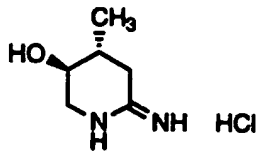
The 5-methoxy-4-methyl-imino-methyl ether was treated with ammonium chloride (32 mg, 0.60 mmol) in refluxing ethanol (4 mL) for 4 h.

The cooled reaction mixture was evaporated, and the resulting solid dried *in vacuo*; yield 61 mg.

^{1}H NMR (400 MHz, CD_3OD): δ 1.08 (dd, 1H); 2.23 (m, 1H); 2.32 (dd, 1H); 2.81 (dd, 1H); 3.38 (dd, 1H); 3.40 (s, 3H); 3.42 (m, 1H); 3.55 (dd, 1H)

Mass spectrum m/e = 143 (m +1).

EXAMPLE 98



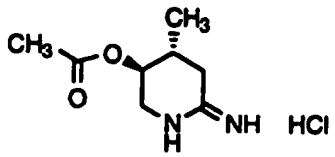
2-Imino-5(S)-hydroxy-4(R)-methyl-piperidine, hydrochloride

The 5-hydroxy-4-methyl-imino-methyl ether from Step E of Example 97 was treated with ammonium chloride (16 mg, 0.30 mmol) in refluxing ethanol (3 mL) for 4 hours. The cooled reaction mixture was evaporated. The solid was taken up in methanol, and the product crystallized out upon addition of diethyl ether; yield 22 mg.

^{1}H NMR (400 MHz, CD_3OD): δ 1.08 (d, 3H); 2.01 (m, 1H); 2.33 (dd, 1H); 2.85 (dd, 1H); 3.19 (dd, 1H); 3.54 (dd, 1H); 3.71 (m, 1H).

Mass spectrum m/e = 128 (M +1).

EXAMPLE 99



2-Imino-5(S)-acetyloxy-4(R)-methyl-piperidine hydrochloride

Step A: 5(S)-Acetyloxy-4(R)-methyl-2-piperidone

5(S)-Hydroxy-4(R)-methyl-2-piperidone (43 mg, 0.33 mmol) was treated with pyridine (0.5 mL) and acetic anhydride (0.3 mL) overnight at room temperature. The mixture was evaporated and coevaporated several times with toluene. Flash silica gel chromatography eluting with 2% methanol/CH_2Cl_2 gave pure title compound; yield 17.7 mg.

^1H NMR (400 MHz, CD_3OD): δ 1.04 (d, 3H); 2.08 (s, 3H); 2.09 (dd, 1H); 2.21 (m, 1H); 2.58 (dd, 1H); 3.22 (dd, 1H); 3.56 (dd, 1H); 4.83 (m, 1H).

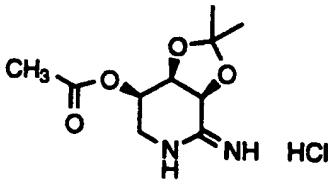
Step B: 2-Imino-5(S)-acetyloxy-4(R)-methyl-piperidine hydrochloride

To a solution of 5(S)-acetyloxy-4(R)-methyl-2-piperidone (17.7 mg, 0.103 mmol) in methylene chloride (1.5 mL) was added trimethyloxonium tetrafluoroborate (16.8 mg, 0.113 mmol). The reaction mixture was stirred for 18 hours at room temperature. The mixture was diluted with ethyl acetate, washed with saturated sodium hydrogencarbonate solution, saturated brine solution, dried ($MgSO_4$), and carefully evaporated (bath temperature <15°C) to avoid loss of the volatile imino ether. The residue was treated with ammonium chloride (4.4 mg, 0.082 mmol) in refluxing ethanol (1.5 mL) for 3 hours. The reaction mixture was evaporated and triturated with ethyl acetate. The resulting solid was filtered, washed with ethyl acetate, and dried *in vacuo*.

^{1}H NMR (400 MHz, CD_3OD): δ 1.09 (d, 3H); 2.08 (s, 3H); 2.26 (m, 1H); 2.45 (dd, 1H); 2.89 (dd, 1H); 3.37 (dd, 1H); 3.69 (dd, 1H).

Mass spectrum m/e = 171 (M +1).

EXAMPLE 100



2-Imino-3(S),4(R)-O-isopropylidene-5(R)-acetyloxy-piperidine hydrochloride

Step A: 3(R),4(R)-O-Isopropylidene-5(R)-acetyloxy-2-piperidone

A solution of 5(R)-azidomethyl-3(R),4(R)-O-isopropylidene-dihydro-2(3H)-furanone [prepared according to Herdeis and Waibel, *Arch. Pharm*: **324**, 269-274 (1991)] (460 mg, 2.16 mmol) in methanol (12 mL) was hydrogenated under a balloon atmosphere of hydrogen gas in the presence of 20% palladium hydroxide on carbon (75 mg) for 4 hours at room temperature. The catalyst was removed by filtration through an Anotop 25 Dispo Syringe Filter (0.2 μm). The filtrate was evaporated, and the resulting solid dried *in vacuo*. The solid was treated with acetic anhydride (2 mL) and pyridine (3 mL) until thin layer chromatography (10% methanol/CH_2Cl_2) indicated complete conversion into a more mobile product. The reaction mixture was evaporated and coevaporated several times with toluene. The product was purified by flash silica gel chromatography eluting with 2-3% methanol/CH_2Cl_2. Pure title compound was obtained as a solid; yield 185 mg (37%).

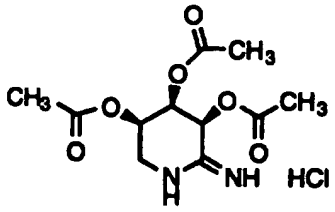
Step B: 2-Imino-3(S),4(R)-O-Isopropylidene-5(R)-acetyloxy-piperidine hydrochloride

To a solution of 3(R),4(R)-O-isopropylidene-5(R)-acetyloxy-2-piperidone (99 mg, 0.432 mmol) in methylene chloride (3 mL) was added trimethyloxonium tetrafluoroborate (70 mg, 0.473 mmol). The reaction mixture was stirred for 18 hours at room temperature. The mixture was diluted with ethyl acetate, washed with saturated sodium hydrogencarbonate solution, saturated brine solution, dried ($MgSO_4$), and carefully evaporated (bath temperature <15°C) to avoid loss of the volatile imino ether. The residue was treated with ammonium chloride (18.4 mg, 0.344 mmol) in refluxing ethanol (4 mL) for 5 hours. The reaction mixture was evaporated, and the residue triturated with a mixture of ethyl acetate and diethyl ether. The solid was filtered, washed with diethyl ether, and dried *in vacuo*.

^1H NMR (400 MHz, CD_3OD): δ 1.44 (s, 3H); 1.48 (s, 3H); 2.08 (s, 3H); 3.48 (dd, 1H); 3.57 (dd, 1H); 4.73 (dd, 1H); 5.00 (d, 1H); 5.32 (m, 1H).

Mass spectrum m/e = 229 (M +1).

EXAMPLE 101



2-Imino-3(S),4(R),5(R)-triacetyloxy-piperidine hydrochloride

Step A: 3(R),4(R),5(R)-Triacetyloxy-2-piperidone

3(R),4(R)-O-Isopropylidene-5(R)-acetyloxy-2-piperidone (80 mg, 0.349 mmol) was treated with 90% aqueous trifluoroacetic acid until thin-layer chromatography (TLC) indicated complete disappearance of starting material.

The reaction mixture was evaporated and coevaporated several times with toluene. The residue was treated with pyridine (1 mL) and acetic anhydride (0.7 mL) until complete conversion into a more mobile product by TLC. The reaction mixture was evaporated and coevaporated several times with toluene. The product was purified by flash silica gel chromatography eluting with 2% methanol/CH_2Cl_2; yield 48.2 mg (51%).

^1H NMR (400 MHz, $CDCl_3$): δ 2.06 (s, 3H); 2.12 (s, 3H); 2.14 (s, 3H); 3.52 (m, 2H); 5.30 (td, 1H), 5.50 (d, 1H); 5.69 (m, 1H); 5.76 (br s, 1H).

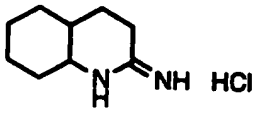
Step B: 2-Imino-3(S),4(R),5(R)-triacetyloxy-piperidine hydrochloride

To a solution of 3(R),4(R),5(R)-triacetyloxy-2-piperidone (46.7 mg, 0.171 mmol) in methylene chloride (2 mL) was added trimethyloxonium tetrafluoroborate (28 mg, 0.189 mmol). The reaction mixture was stirred for 18 hours at room temperature. The mixture was diluted with ethyl acetate, washed with saturated sodium hydrogencarbonate solution, saturated brine solution, dried ($MgSO_4$), and carefully evaporated (bath temperature <15°C) to avoid loss of the volatile imino ether. The residue was treated with ammonium chloride (6.8 mg, 0.127 mmol) in refluxing ethanol (2.5 mL) for 4 hours. The reaction mixture was evaporated, and the resulting solid dried *in vacuo*.

^1H NMR (400 MHz, CD_3OD): δ 2.03 (s, 3H); 2.09 (s, 3H); 2.12 (s, 3H); 3.43 (dd, 1H); 3.51 (dd, 1H); 5.40 (m, 1H); 5.61 (d, 1H); 5.68 (m, 1H).

Mass spectrum m/e = 274.

EXAMPLE 102



cis-Decahydro-2-iminoquinoline hydrochloride

Step A: cis-Octahydroquinolin-2(1H)-one

A suspension of 1g of 3,4,5,6,7,8-hexahydro-2(1H)-quinolinone in 1:1 mixture of dioxane and ethanol was hydrogenated in presence of 250 mg of 10% palladium on carbon at 60 psi and room temperature for 4 hours. The catalyst was filtered on a bed of filter cel and washed with dioxane-ethanol mixture. The filtrate was concentrated to give a residue which was purified on silica gel using ethyl acetate as solvent to give 510 mg of the desired product containing about 10% trans-isomer. Recrystallization from hexane did not improve the isomer ratio.

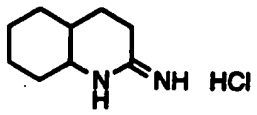
^{1}H NMR ($CDCl_3$): 3.49(m,1H); 2.33(m,2H)1.2-2.0(m,11H)

Step B: *cis*-Decahydro-2-iminoquinoline hydrochloride

The title compound was synthesized as described in examples 2 and 3 from cis-octahydroquinolin-2(1H)-one.

^{1}H NMR (DMSO): 3.49(m,1H); 2.53(m,2H); 1.25-2.0(m,11H); 8.16(b,1H); 8.7(b,1H); 9.65(b,1H)

EXAMPLE 103



trans-Decahydro-2-iminoquinoline hydrochloride

Step A: *trans*-Octahydroquinolin-2(1H)-one

A mixture of 1g (6.62 mmol) of 3,4,5,6,7,8,-hexahydro-2(1H)-quinolinone, 2.8g (41 mmol) of sodium formate and 5 mL of formic acid was heated to reflux for 1 day The reaction mixture was then cooled and 20% sodium hydroxide solution was added to make it basic. This mixture was then extracted with ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous magnesium sulfate and the solvent was removed to give a crude product. This was purified on silica gel using ethyl acetate as solvent to provide 752 mg of the desired product with about 10% of the cis- isomer. Recrystallization of this material from cyclohexane did not improve the ratio of the isomers.

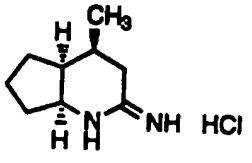
^{1}H NMR ($CDCl_3$): 2.88(m,1H); 2.4(m,2H)1.0-1.9(m,11H)

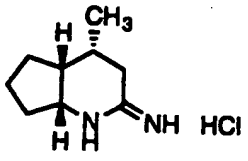
Step B: *trans*-Decahydro-2-iminoquinoline hydrochloride

The title compound was synthesized from trans-octahydroquinolin-2(1H)-one as described in examples 2 and 3.

^{1}H NMR (DMSO): 2.95(m,1H); 2.58(m,2H); 1.0-2.0(m,11H); 8.12(b,1H); 8.76(b,1H); 9.70(b,1H)

EXAMPLE 104





4(S)-Methyl-4a(S),7a(S)-perhydro-2-imino-1-pyrindine hydrochloride and 4(R)-Methyl-4a(R),7a(R)-perhydro-2-imino-1-pyrindine hydrochloride

Step A: 4(R+S)-Methyl-4a(R+S),7a(R+S)-perhydro-1-pyrindin-2-one:

A mixture of 1 g of 2-hydroxy-4-methyl-6,7-dihydro-5H-1-pyrindine (prepared according to A. Sakurai and H. Midorikawa, Bull Chem Soc Japan, 41, 165, 1968) and platinum oxide (0.5g) in 50 mL of glacial acetic acid was hydrogenated on a Parr shaker at room temperature and 50 psi for 2 days. The catalyst was filtered and washed with acetic acid. The filtrate was concentrated to give the desired lactam as a white solid after purification on silica gel using 2% methanol in ethyl acetate as solvent.

Step B: 4(S)-Methyl-4a(S),7a(S)-perhydro-1-pyrindin-2-one and 4(R)-Methyl-4a(R),7a(R)-perhydro-1-pyrindin-2-one:

The mixture of enantiomers obtained from the step A was separated into its chiral components using ChiralCel OD column using 90:10 hexane:isopropanol mixture as solvent on HPLC. The faster moving enantiomer was 4(S)-methyl-4a(S),7a(S)-perhydro-1-pyrindin-2-one and the slower moving enantiomer was 4(R)-methyl-4a(R),7a(R)-perhydropyrindin-2-one.

^{1}H NMR ($CDCl_3$): 5.45(b,1H); 3.8(m,1H);1.4-2.3(m,10H); 0.96(d,3H)

Step C: 4(S)-Methyl-4a(S),7a(S)-perhydro-2-imino-1-pyrindine hydrochloride and 4(R)-Methyl-4a(R),7a(R)-perhydro-2-imino-1-pyrindine hydrochloride

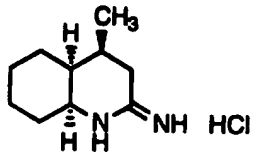
The title compounds were prepared according to the method described in Examples 2 and 3. The stereochemical assignments for these two compounds were confirmed by x-ray structure determination.

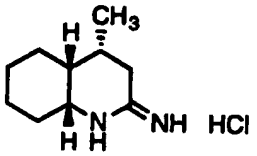
^{1}H NMR (CD_3OD): 3.9(m,1H); 1.4-2.5(m, 1H); 1.06(d,3H)

4(S)-Methyl-4a(S),7a(S)-perhydro-2-imino-1-pyrindine hydrochloride specific rotation = +53.95° (c = 0.215, EtOH)

4(R)-Methyl-4a(R),7a(R)-perhydro-2-imino-1-pyrindine hydrochloride specific rotation = -54.55° (c = 0.22, EtOH)

EXAMPLE 105





4(S)-Methyl-4a(S),8a(S)-decahydro-2-iminoquinoline hydrochloride and 4(R)-Methyl-4a(R),8a(R)-decahydro-2-iminoquinoline hydrochloride

Step A: 4(R+S)-Methyl-4a(R+S),8a(R+S)-decahydroquinoline-2-one:

A mixture of 2-hydroxy-4-methyl quinoline (1g) and platinum oxide (0.5g) in 50 mL of glacial acetic acid was hydrogenated on a Parr shaker at room temperature and 50 psi for 2 days. The catalyst was filtered and washed with acetic acid. The filtrate was concentrated to give the desired lactam as a white solid after purification on silica gel using 2% methanol in ethyl acetate as solvent.

Step B: 4(S)-Methyl-4a(S),8a(S)-decahydroquinolin-2-one and 4(R)-Methyl-4a(R),8a(R)-decahydroquinolin-2-one:

The mixture of enantiomers obtained from the step A was separated into its chiral components using ChiralCel OD column using 90:10 hexane:isopropanol mixture as solvent on HPLC. The faster moving enantiomer was 4(S)-methyl-4a(S),8a(S)-decahydroquinolin-2-one and the slower moving enantiomer was 4(R)-methyl-4a(R),8a(R)-decahydroquinolin-2-one.

^{1}H NMR ($CDCl_3$): 5.42(b,1H); 3.6(m,1H); 2.3(m,1H); 2.0(m,1H); 1.1-1.7(m,8H); 0.96(d,3H)

Step C: 4(S)-Methyl-4a(S),8a(S)-decahydro-2-iminoquinoline hydrochloride and 4(R)-Methyl-4a(R),8a(R)-decahydro-2-iminoquinoline hydrochloride

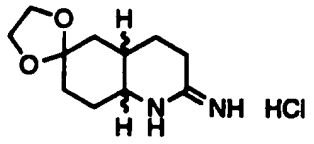
The title compounds were prepared according to the method described in Examples 2 and 3 and the assignment of stereochemistry was confimed by x-ray crystal structure determination.

^{1}H NMR (CD3OD): 3.68(m,1H); 2.6(m, 1H); 2.3(m,1H); 2.1(m,1H); 1.25-1.96(m,9H); 1.04(d,3H)

4(S)-Methyl-4a(S),8a(S)-decahydro-2-iminoquinoline hydrochloride specific rotation = +12.31° (c = 0.195, EtOH)

4(R)-Methyl-4a(R),8a(R)-decahydro-2-iminoquinoline hydrochloride specific rotation = -12.5° (c = 0.2, EtOH)

EXAMPLE 106



2-Imino-octahydro-quinolin-6(5H)-one-6-ethylene ketal hydrochloride

Step A: 3,4,7,8-Tetrahydro-quinolin-2(1H)-6(5H)-dione-6-ethylene ketal

A solution of 1,4-cyclohexanedione monoethylene ketal (10 g, 0.64 mol) and pyrrolidine (11.6 mL, 0.13 mol) in toluene (50 mL) was heated at reflux for 2 h collecting water in a Dean-Stark trap. Half the volume was distilled off and the reaction cooled to room temperature. To the mixture was added a solution of acrylamide (10.9 g, 0.15 mol) in N,N-dimethylacetamide (25 mL) and the mixture heated at 78 °C for 18 h and 135 °C for 4 h. The reaction was cooled, water (100 mL) was added

and the mixture stirred 0.5h. The mixture was extracted with methylene chloride, dried (Na_2SO_4), and evaporated. The solid was triturated with ether, collected and dried to give the title compound.

^1H NMR ($CDCl_3$): δ 1 -2.65 (m,10H); 3.88-4.05 (m,4H); 4.80 (m,4H); 7.70 (b,1H)

Mass spectrum m/e = 2 (M+1)

Step B: 3,4,4a,7,8,8a-Hexahydro-quinolin-2(1H)-6(5H)-dione-6-ethylene ketal

A suspension of 3,4,7,8-tetrahydro-quino (1H)-6(5H)-dione-6-ethylene ketal (0.5 g, 2.39 mmol) in ethanol (L) in the presence of 5% rhodium / alumina (0.5 g) was hydrogenated at 50 psi for 2.5 h. The catalyst was removed by filtration through Celite and evaporated to give the title compound.

^1H NMR (400 MHz, $CDCl_3$): δ 1.45-2.45 (m,11H); 3.55 (m,1H); 3.94 (m,4H); 5.74 (b,1H); 5.95 (b,1H)

Mass spectrum m/e = 212 (M+1)

Step C: 2-Imino-octahydro-quinolin-6(5H)-one-6-ethylene ketal hydrochloride

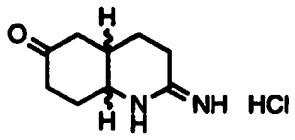
To a solution of 3,4,4a,7,8,8a-hexahydro-quinolin-2(1H)-6(5H)-dione-6-ethylene ketal (100 mg, 0.47 mmol) in methylene chloride (2 mL) was added trimethyloxonium tetrafluoroborate (77 mg, 0.52 mmol) and the mixture stirred at room temperature for 18 h. The reaction mixture was diluted with ethyl acetate (25 mL), neutralized with saturated sodium carbonate, the aqueous layer washed with ethyl acetate, and the combined organics washed with brine, dried (Na_2SO_4) and evaporated below room temperature to give a crude oil. The oil was taken

up in ethanol (2ml), ammonium chloride (18mg, 0.33mmol)was added and the mixture refluxed for 3 h. The reaction mixture was evaporated to dryness, the residue triturated with ethyl acetate and purified by flash chromatography using (80:20:2) acetonitrile: water: acetic acid as eluant to yield the title compound.

^{1}H NMR (400 MHz, CD_3OD): δ 1.60-2.73 (m,11H); 3.63 (m,1H); 3.93 (m,4H)

Mass spectrum m/e = 211 (M+1)

EXAMPLE 107



2-Imino-octahydro-quinolin-6(5H)-one hydrochloride

Step A: Hexahydro-quinolin-2(1H),6(5H)-dione

A solution of 3,4,4a,7,8,8a-hexahydro-quinolin-2(1H)-6(5H)-dione-6-ethylene ketal (prepared as described in Example 106,Step B), (300 mg, 1.42 mmol) in 80% acetic acid / water (8 mL) was heated at 65 °C for 1 h, evaporated to dryness, and coevaporated with toluene to give a solid. Purification was accomplished by flash silica gel chromatography using 3% methanol / methylene chloride as eluant to give the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60-2.50 (m, 11H); 3.78 (m,1H); 6.60 (b,1H)

Mass spectrum m/e = 168 (M+1)

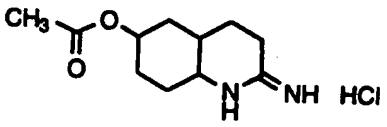
Step B: 2-Imino-octahydro-quinolin-6(5H)-one hydrochloride

The above compound was prepared in a similar fashion as Example 106, Step C, but substituting hexahydro-quinolin-2(1H),6(5H)-dione in place of 3,4,4a,7,8,8a-hexahydro-quinolin-2(1H)-6(5H)-dione-6-ethylene ketal to yield the title compound.

^{1}H NMR (400 MHz, CD_3OD): δ 1.70-2.64 (m,10H); 2.73 (m,1H); 3.97 (m,1H)

Mass spectrum m/e = 167 (M+1)

EXAMPLE 108



2-Imino-6-acetyloxy-*cis*-decahydroquinoline hydrochloride

Step A: cis-3,4,4a,7,8,8a-Hexahydro-quinolin-2(1H)-6(5H)-dione-6-ethylene ketal

The above compound was prepared in a similar fashion as Example 106, Step B, but was fractionally crystallized from ethyl acetate to give greater than 96% cis isomer as the title compound.

400MHz ^{1}H NMR ($CDCl_3$): δ 1.45-2.45 (m, 11H); 3.55 (m, 1H); 5.80 (b, 1H)

Step B: cis-Hexahydro-quinolin-2(1H),6(5H)-dione

The above compound was prepared in a similar fashion as Example 107, Step A, to give the title compound.

^{1}H NMR ($CDCl_3$): δ 1.70-2.50 (m, 11H); 3.78 (m, 1H); 6.57 (b, 1H)

Step C: 6-Hydroxy-cis-(4a,8a)-octahydro-quinolin-2(1H)-one

To a solution of cis-hexahydro-quinolin-2(1H),6(5H)-dione (50 mg, 0.30 mmol) in methanol (1 ml) cooled to 0 °C was added sodium borohydride (11 mg, 0.30 mmol) and the solution stirred for 0.5 h. Water (0.25 ml) was added and the reaction mixture was evaporated to give the crude title compound.

^{1}H NMR (400 MHz, CD_3OD): δ 1.32-2.00 (m,10H); 2.28 (m,2H); 3.54 (m,1H); 3.64 (m,1H)

Step D: 6-Acetyloxy-cis-(4a,8a)-octahydro-quinolin-2(1H)-one

To a mixture of crude 6-hydroxy-cis-(4a,8a)-octahydro-quinolin-2(1H)-one (203 mg, 0.86 mmol) in methylene chloride (5 mL), was added pyridine (2.8 mL), acetic anhydride (1.4 mL), and 4-dimethylaminopyridine (23 mg). After 6 h the reaction mixture was diluted with methylene chloride (50 mL), washed with water, saturated sodium bicarbonate, brine, dried (Na_2SO_4), and evaporated to give a pale yellow solid. It was subjected to flash chromatography using 2% methanol / methylene chloride as eluant to give the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56-2.02 (m, 12H); 2.35 (m, 2H); 3.55 (m, 1H); 4.75 (m,1H); 5.74 (b,1H)

Mass spectrum m/e = 212 (M+1)

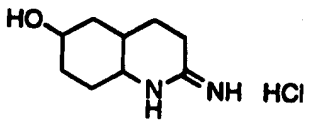
Step E: 2-Imino-6-acetyloxy-*cis*-decahydroquinoline hydrochloride

The above compound was prepared in a similar fashion as Example 106, Step C, but substituting 6-acetyloxy-cis-(4a,8a)-octahydro-quinolin-2(1H)-one in place of 3,4,4a,7,8,8a-hexahydro-quinolin-2(1H)-6(5H)-dione-6-ethylene ketal to yield the title compound.

^{1}H NMR (400 MHz, CD_3OD): δ 1.50-2.20 (m,12H); 2.65 (m,2H); 3.64 (m,1H); 4.80 (m,1H)

Mass spectrum m/e = 211 (M+1)

EXAMPLE 109



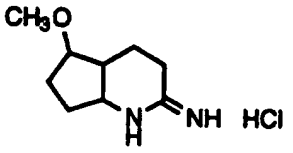
2-Imino-6-hydroxy-*cis*-decahydroquinoline hydrochloride

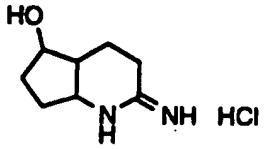
Ammonia gas was bubbled to a solution of 2-imino-6-acetyloxy-cis-decahydroquinoline hydrochloride, prepared previously as described in Example 108, Step E, (38 mg, 0.15 mmol) in methanol (2 ml) at 0 °C for 5 min. The reaction flask was stoppered and stirred at 0 °C for 3 h and at room temperature for 72 h. The reaction was evaporated to dryness and purified by flash chromatography using (80:16:2) acetonitrile: water: acetic acid as eluant to give the title compound.

^{1}H NMR (400 MHz, CD_3OD): δ 1.28-2.13 (m,10H); 2.63 (m,2H); 3.60 (m,1H); 3.68 (m, 1H)

Mass spectrum m/e = 169 (M+1)

EXAMPLES 110,111





2-Imino-5-methoxy-cis-perhydro-pyrindene hydrochloride (Example 110) and 2-imino-5-hydroxy-cis-perhydro-pyrindene hydrochloride (Example 111)

Step A: 3,4,6,7-Tetrahydro-pyrindene-2(1H)-5-dione

A mixture of 1,3-cyclopentanedione (20 g, 0.20 mol), acrylamide (29 g, 0.41 mol), and p-toluenesulfonic acid monohydrate (2.3 g, 0.01 mol) in N,N-dimethylacetamide (20 mL) was heated at 85 °C for 18 h and 150 °C for 3 h. The reaction mixture was cooled, water (100 mL) was added and stirred for 0.5 h. Methylene chloride (100 mL) was added, the layers were separated, the aqueous layer washed with methylene chloride, the combined organics dried (Na_2SO_4) and evaporated to give a gum. Purification by flash chromatography using 2% methanol / methylene chloride as eluant gave the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.52 (m, 4H); 2.62 (m, 4H); 8.32 (b, 1H)

Mass spectrum m/e = 152 (M+1)

Step B: 5-Hydroxy-cis-perhydro-pyrinden-2(1H)-one

A suspension of 3,4,6,7-tetrahydro-pyrindene-2(1H)-5-dione (2.8 g, 0.19 mol) in ethanol (150 mL) in the presence of 5% rhodium / alumina was hydrogenated at 50 psi for 18 h. The catalyst was removed by filtration through Celite and evaporated to give the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.69-1.95 (m, 7H); 2.14-2.33 (m, 2H); 2.47 (m, 1H); 3.74 (m, 1H); 4.33 (m,1H); 4.33 (m,1H); 6.04 (b, 1H)

Compound A: 2-Imino-5-methoxy-cis-perhydro-pyrindene hydrochloride
Compound B: 2-Imino-5-hydroxy-cis-perhydro-pyrindene hydrochloride

The above compounds were prepared in a similar fashion as Example 106, Step C, but substituting 5-hydroxy-cis-perhydro-pyrinden-2(1H)-one in place of 3,4,4a,7,8,8a-hexahydro-quinolin-2(1H)-6(5H)-dione-6-ethylene ketal. Purification by flash chromatography using (80: 8: 2) acetonitrile: water: acetic acid as a eluant separated the above two title compounds A and B;

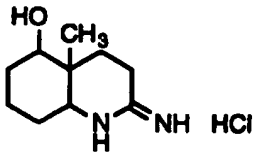
Compound A: ^{1}H NMR (400 MHz, CD_3OD): δ 1.70-2.10 (m,8H); 2.47 (m,3H); 2.70 (m,1H); 3.85 (m, 2H)

Mass spectrum m/e = 169 (M+1)

Compound B: ^{1}H NMR (400 MHz, CD_3OD): δ 1.70-2.10 (m,7H); 2.34-2.52 (m,2H); 2.75 (m,1H); 3.85 (m,1H); 4.29 (m,1H)

Mass spectrum m/e = 155 (M+1)

EXAMPLE 112



EXAMPLE 112

L-776,009-001V
2-Imino-5-hydroxy-4a-methyl-trans-(4a,8a)-decahydroquinoline hydrochloride

Step A: 4a-Methyl-3,4,6,7-tetrahydro-quinolin-2(1H),5(4aH)-dione

The title compound was obtained from 2-methylcyclohexane-1,3-dione and acrylamide by the method described in example 110, step A.

^{1}H NMR ($CDCl_3$): 7.77 (br, 1H), 5.14 (dd, 1 H), 2.78 (m, 1H), 2.58 (m, 2H), 2.53 (m, 1H), 2.43 (m, 2H), 2.04 (m, 1H), 1.80 (m, 1H), 1.38 (s, 3H).

Mass spectrum m/e = 180 (M+1)

Step B: 5-Hydroxy-4a-methyl-trans-(4a,8a)-octahydro-quinolin-2(1H)-one

The title compound was obtained from 500 mg of 4a-methyl-3,4,6,7-tetrahydro-quinolin-2(1H),5(4aH)-dione by the method described in example 110, step B with the following additions: The crude solid was purified by silica gel chromatography on a 21 x 130 mm column eluting a gradient from 0 to 5% methanol in methylene chloride to afford 185 mg of the title compound.

^{1}H NMR ($CDCl_3$): 5.64 (br, 1H), 3.37 (dt, 1H), 3.08 (dd, 1H), 2.47 (m, 2H), 2.11 (m, 1H), 1.80 (m, 2H), 1.57 (m, 2H), 1.46 (m, 4H), 0.95 (s, 3H).

Mass spectrum m/e = 184 (M+1)

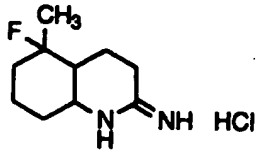
Step C: 2-Imino-5-hydroxy-4a-methyl-trans-(4a,8a)-decahydroquinoline hydrochloride

The title compound was obtained from 180 mg of 5-hydroxy-4a-methyl-trans-(4a,8a)-octahydro-quinolin-2(1H)-one by the method described in examples 2 and 3.

^{1}H NMR (CD_3OD): 3.36 (dt, 1H), 3.12 (dd, 1H), 2.70 (dd, 2H), 2.08 (m, 1H), 1.83 (m, 1H), 1.70 (m, 2H), 1.57 (m, 2H), 1.44 (m, 2H), 0.87 (s, 3H).

Mass spectrum m/e = 183 (M+1)

EXAMPLE 113



2-Imino-5-fluoro-5-methyl-cis-(4a,8a)-decahydroquinoline hydrochloride

Step A: 5-Fluoro-5-methyl-cis-(4a,8a)-octahydro-quinolin-2(1H)-one

To a solution of 150 mg (0.82 mmol) of 5-hydroxy-4a-methyl-trans-(4a,8a)-octahydro-quinolin-2(1H)-one in 2 mL methylene chloride at 0 °C was added 0.108 mL (0.82 mmol) diethylaminosulfur trifluoride dropwise. After stirring for one hour, apply reaction mixture directly to a 21 x 300 mm silica column and purify by eluting with 20% acetone/methylene chloride to afford 55 mg of the title compound as a 4:1 mixture of cis:trans diastereomers.

^{1}H NMR ($CDCl_3$): 6.19 (br, 1H), 3.31 (dt, 1 H), 2.51 (m, 1H), 2.28 (m, 1H), 2.21-1.90 (m, 5H), 1.85-1.50 (m, 4H), 1.40 (d, J = 22 Hz, 3H).

Mass spectrum m/e 186 (M+1)

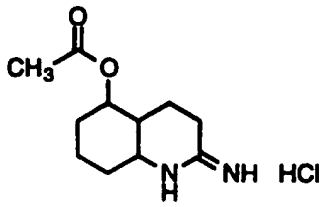
Step B: 2-Imino-5-fluoro-5-methyl-cis-(4a,8a)-decahydroquinoline hydrochloride

The title compound was obtained from 55 mg of 5-fluoro-5-methyl-cis-(4a,8a)-octahydro-quinolin-2(1H)-one by the method described in Examples 2 and 3.

^{1}H NMR (CD_3OD): 3.57 (dt, 1H), 2.67 (m, 2H), 2.20 (m, 2H), 2.08 (m, 1H), 1.95 (m, 1H), 1.88-1.68 (m, 5H), 1.44 (d, J = 23 Hz, 3H).

Mass spectrum m/e = 185 (M+1)

EXAMPLE 114



5-Acetoxy-2-imino-cis-(4a,8a)-decahydroquinoline hydrochloride

Step A: 5-Acetoxy-cis-(4a,8a)-octahydroquinolin-2(1H)-one

To a solution of 100 mg (0.59 mmol) of 5-hydroxy-cis-(4a,8a)-octahydroquinolin-2(1H)-one (prepared as shown in Example 110, Step A and B) in 1 mL pyridine at 25 °C was added 0.046 mL (0.65 mmol) acetic anhydride and 8 mg dimethylaminopyridine. After stirring for 16 hours, apply reaction mix directly to a 21 x 130 mm silica column and purify by eluting a gradient from 0 to 5% methanol/methylene chloride to afford 80 mg of the title compound as a cis racemate.

^{1}H NMR ($CDCl_3$): 6.19 (br, 1H), 4.88 (m, 1H), 3.41 (m, 1 H), 2.47 (m, 1H), 2.35 (m, 2H), 2.05 (s, 3H), 1.77 (m, 5H), 1.45 (m, 2H), 1.30 (m, 1H).

Mass spectrum m/e = 212 (M+1)

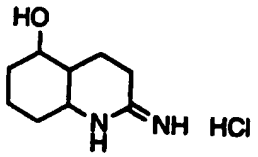
Step B: 5-Acetoxy-2-imino-cis-(4a,8a)-decahydroquinoline hydrochloride

The title compound was obtained from 80 mg of 5-acetoxy-cis-(4a,8a)-octahydroquinolin-2(1H)-one by the method described in examples 2 and 3.

^{1}H NMR (CD_3OD): 4.94 (dt, 1H), 3.59 (dt, 1H), 2.73 (dt, 1H), 2.62 (m, 1H), 2.40 (m, 1H), 2.04 (s, 3H), 1.89 (m, 2H), 1.86-1.71 (m, 4H), 1.53 (m, 2H).

Mass spectrum m/e = 211 (M+1)

EXAMPLE 115



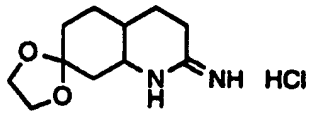
5-Hydroxy-2-imino-cis-(4a,8a)-decahydroquinoline hydrochloride

To a solution of 30 mg (0.14 mmol) of 5-acetoxy-2-imino-cis-(4a,8a)-decahydroquinoline hydrochloride in 1 mL methanol at 0 °C was added ammonia gas by bubbling in through a needle. After stirring for 64 hours, apply reaction mix directly to a 8 x 50 mm silica column and purify by eluting 80:16:4 acetonitrile/water/acetic acid to afford 15 mg of the title compound as a cis racemate.

^{1}H NMR (CD_3OD): 3.80 (dt, 1H), 3.52 (dt, 1H), 2.74 (dt, 1H), 2.58 (m, 1H), 2.21 (m, 1H), 1.93 (m, 2H), 1.77 (m, 2H), 1.66 (m, 2H), 1.35 (m, 2H).

Mass spectrum m/e = 169 (M+1)

EXAMPLE 116



2-Imino-octahydroquinolin-7(8H)-one-7-ethylene ketal hydrochloride

Step A: γ-Acetyl-γ-ethoxypimelonitrile

To a 50 mL round bottom flask fitted with a Teflon stirrer were added 13 gm (100 mmol) of ethyl acetoacetate, 15 mL of tert-butanol and 7.5 mL of benzyltrimethylammonium hydroxide (Triton B™, 40 % by weight) in methanol. The solution was cooled to 4 °C with ice and added dropwise over 10 min 10.6 g (100 mmol) of acrylonitrile keeping the solution temperature <20 °C. The reaction was stirred for 4 h at 25 °C. The product falls out of solution and the mixture became a solid mass. Cold water (100 mL) was added to suspend the precipitate and filtered. The crystalline product was washed with 2X 20 mL of ice water and dried under reduced pressure at 60 °C overnight to recover 18.5 g (78%) of product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30(t, 3H, J=7 Hz); 2.1-2.4(m, 8H); 2.19 (s, 3H); 4.27 (q, 2H, J=7 Hz).

Step B: 3,4,4a,5-Tetrahydroquinolin-2(1H)-7(6H)-dione

This procedure is taken from C. F. Koelsch et al. *J. Am. Chem. Soc.*, 1959, **72**, 346. γ-Acetyl-γ-ethoxypimelonitrile (18.5 g) was treated with a hot solution (120 °C) of 41 mL of concentrated sulphuric acid and 18 mL of water. After heating at 140 °C for 15 min, the solution was poured into 200 mL of ice water with mechanical stirring

and added $CaCO_3$ until the pH> 6.0. The precipitated $CaSO_4$ was filtered and washed with 3X 100 mL of water. The water was removed under reduced pressure and the residue was recrystallized from boiling water to recovered 4.5 g (36%) of product; (Lit. yield= 42%). mp=233-235 °C (Lit = 234-235 °C).

^1H NMR 400 MHz($CDCl_3$) δ 1.55-1.85(m, 2H); 2.0-2.1(m, 1H); 2.15-2.25 (m, 1H); 2.35-2.7 (m, 5H); 5.40 (s, 1H); 7.90 (bs, 1H).

Step C: 3,4,4a,5-Tetrahydro-quinolin-2(1H),7(6H)-dione,7-ethyleneketal

A mixture of the vinylogous imide 3,4,4a,5-tetrahydroquinolin-2(1H)-7(6H)-dione (1.30 gm, 7.9 mmol) , ethylene glycol (4.7 mL), *p*- toluenesulphonic acid (100 mg), and benzene (200 mL) was heated under reflux with stirring using a Dean Stark water separator for 40 h. After the solvent was removed under reduced pressure, the resulting residue was extracted with chloroform. The extract was washed with saturated $NaHCO_3$ and brine, evaporated to give a solid which was chromatographed on silica gel (95/5 - CH_2Cl_2/ MeOH). Chromatography gave 980 mg of product. Yield=60%.

^1H NMR (400 MHz, $CDCl_3$) δ 1.7-1.8(m, 3H); 2.0-2.1(m, 1H); 2.1-2.2 (m, 5H); 2.4-2.5(m, 2H); 3.97 (s, 4H); 7.28 (bs, 1H).

Step D: Hexahydro-quinolin-2(1H),7(8H)-dione,7-ethyleneketal

The product of step C (980 mg, 4.7 mmol) was hydrogenated over 5% Rhodium/alumina (1.0 g) in 10 mL of ethanol at 50 psi for 18 h. The catalyst was filtered from the solution and the filtrate evaporated under reduced pressure. The solid was chromatographed on silica gel (97/3 - CH_2Cl_2/ MeOH) and 570 mg of the desired product was recovered along with 150 mg of starting material, mp=171-173°.

^{1}H NMR 400 MHz($CDCl_3$) δ 1.4-2.3 (m, 9H); 2.4-2.55(m, 2H); 3.75(m, 1H); 3.9 (bs, 4H); 6.2 (bs, 1H).

Step E: 2-Methoxy-hexahydro-quinolin-7(8H)-one-7-ethyleneketal

In a 10 mL round bottomed flask fitted with a stirrer bar were added 100 mg of 3Å molecular sieves (Linde), 4 mL of methylene chloride and 162 mg of trimethyloxonium tetrafluoroborate (1.1 mmol) and cis-octahydro-quinoline-2-one,7-ethyleneketal (211 mg, 1.0 mmol). The mixture was stirred under N_2 for 4 h at 22 °C. The solution was diluted with 10 mL of CH_2Cl_2 and washed with 2 x 5 mL of 5% $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Recovered 190 mg of a cream colored solid which by NMR was the desired product.

^{1}H NMR 400 MHz($CDCl_3$) δ 1.3-1.65(m, 5H); 1.8-1.9(m, 3H); 2.03(ddd, 1H, J=14Hz, J=7Hz, J=3Hz); 2.2 (m, 2H); 3.61 (s, 3H); 3.77(bd, 1H); 3.9-4.0 (m, 4H).

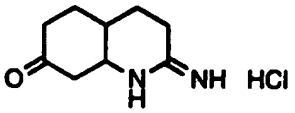
Step F: 2-Imino-octahydroquinolin-7(8H)-one-7-ethylene ketal hydrochloride

In a 25 mL glass pressure bottle fitted with a Teflon stirring bar were added iminoether (180 mg, 0.8 mmol), ammonium chloride (39 mg, 0.72 mmol) and 2 mL of ethanol. The tube was sealed and heated at 100 °C overnight. The solvent was removed in vacuo and added ethyl acetate when the product precipitated. The solid was filtered and dried to recover 120 mg of the hydrochloride salt.

^{1}H NMR 400 MHz(CD_3OD) δ 1.55-1.62(m, 1H); 1.63-1.88(m, 5H); 1.925 (d, 1H, J=2Hz); 1.936 (d, 1H, J=2Hz);2.1(m, 1H,); 2.65(dt, 2H, J=10 Hz, J=2.5 Hz); 3.77 (m, 1H).

Mass Spectrum m/e = 207 (M+1).

EXAMPLE 117



2-Imino-octahydro-quinolin-7(8H)-one hydrochloride

Step A: cis-Octahydroquinolin-2(1H),7(8H)-dione

Hexahydro-quinolin-2(1H),7(8H)-dione,7-ethyleneketal (160 mg, 76 mmoL) was suspended in 5 mL of 2N HCl and stirred overnight at room temperature. Then solid K_2CO_3 was added to neutralize the solution. The solvent was removed under reduced pressure and the residue extracted with chloroform. The $CHCl_3$ solution was concentrated under reduced pressure and the residue recrystallized from EtOAc and hexane. Recovered 110 mg of product.

^1H NMR (400 MHz, $CDCl_3$) δ 1.8-2.1(m, 5H); 2.3-2.45(m, 5H); 1.65 (dd, 1H, J=17Hz, J=6H); 3.95(m, 1H); 6.15 (bs, 1H).

Step B: 2-Methoxy-hexahydro-quinolin-7(8H)-one

This product was made by the procedure described for step E of example 116.

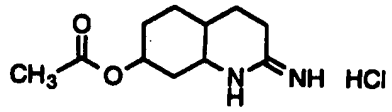
^1H NMR (400 MHz, $CDCl_3$) δ 1.75-1.9(m, 4H): 2.1-2.17(m, 1H); 2.19 (t, 1H, J=6Hz); 2.30(t, 1H, J=6 Hz); 2.41 (dd,1H, J=16 Hz, J=7 Hz); 2.67 (dd,1H, J=14 Hz, J=5 Hz); 3.58 (s, 1H); 3.89 (m, 1H).

Step C: 2-Imino-octahydro-quinolin-7(8H)-one hydrochloride

This product was made by the procedure described for step F of example 116.

^{1}H NMR (400 MHz, CD_3OD) δ 1.9-2.0(m, 3H); 2.04(m, 1H, J=7Hz); 2.4-2.5 (m, 3H); 2.58(dd, 1H, J=12 Hz, J=7 Hz); 2.65-2.8 (m, 3H); 4.0-4.07 (m, 1H).

EXAMPLE 118



7-Acetyloxy-2-imino-trans-(4a,8a)-decahydroquinoline hydrochloride

Step A: 7-Hydroxy-octahydro-trans-(4a,8a)-quinolin-2(1H)-one

3,4,4a,5-Tetrahydroquinolin-2(1H)-7(6H)-dione (2.92g, 17 mmol) was added to a small Parr pressure bottle with 220 mg of platinum oxide and 75 mL of acetic acid. The solution was pressurized to 50 psi with H_2 and shaken for 18 h. The catalyst was removed by filtration and the acetic acid stripped off under reduced pressure. Two major products were observed by TLC (97/3 CH_2Cl_2/MeOH). The lower Rf material, a mixture of 4a,8a- cis and trans ring junction 7-ol's (400 mg) was isolated by column chromatography (97/3 CH_2Cl_2/MeOH). This material was further purified by recrystallization from ethyl acetate whereupon the trans-4a,8a-ring junction -7-ol crystallized out of solution (7-OH configuration unknown).

^{1}H NMR 400 MHz($CDCl_3$) δ 1.05-1.15(m, 1H); 1.2-1.7(m, 5H); 1.7-1.8 (m, 2H,); 1.95-2.15 (m, 2H); 2.3-2.5 (m, 2H); 2.65 (bs, 1H, -OH); 2.95 (m, 1H); 3.7 (m, 1H); 6.45 (bs, 1H).

Step B: 7-Acetyloxy-octahydro-trans-(4a,8a)-quinolin-2(1H)-one

7-Hydroxy-octahydro-trans-(4a,8a)-quinolin-2(1H)-one (89 mg, 0.82 mmol) was dissolved in 5 mL of pyridine. After cooling to 4 °C acetyl chloride (116 µL) was added dropwise with stirring. The reaction was stirred 20 minutes, the solvent was removed in vacuo, then added 10 mL of CH_2Cl_2 and washed with 2x2 mL of 2 N HCl. The organic layer was dried over $MgSO_4$. The filtrate was reduced in volume and chromatographed (97/3 CH_2Cl_2/MeOH) to give 51 mg of the title compound.

^1H NMR (400 MHz, $CDCl_3$) δ 1.2(dq, 1H, J=12 Hz, J=3Hz); 1.3-1.5(m, 5H); 1.75-1.85 (m, 2H,); 2.01 (s, 3H); 2.0-2.05 (m,1H); 2.1-2.15 (m, 1H); 2.3-2.5 (m, 2H); 3.0 (m, 1H); 4.7 (m, 1H); 6.25 (bs, 1H).

Step C: 7-Acetyloxy-2-methoxy-octahydro-trans-(4a,8a)-quinoline

7-Acetyloxy-octahydro-trans-(4a,8a)-quinolin-2(1H)-one was converted to the above compound as previously described in step E of example 116.

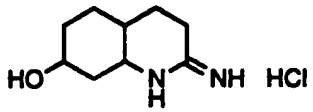
^1H NMR (400 MHz, $CDCl_3$) δ 1.0-1.2(m, 2H); 1.22-1.35(m, 1H); 1.35-1.45 (m, 2H,); 1.72-1.8(m, 2H); 2.02 (s, 3H); 2.2-2.3 (m, 2H); 2.4-2.5 (m,1H); 2.85-2.9 (m, 1H); 2.95 (m, 1H); 3.61 (s, 3H); 4.82 (m, 1H).

Step D: 7-Acetyloxy-2-imino-trans-(4a,8a)-decahydroquinoline hydrochloride

7-Acetyloxy-2-methoxy-octahydro-trans-(4a,8a)-quinoline was converted to the title compound as prevously described in step F of example 116.

^1H NMR (400 MHz, CD_3OD) δ 1.25-1.35(m, 1H); 1.4-1.55 (m, 4H,); 1.85-1.95(m, 2H); 2.02 (s, 3H); 2.0-2.15 (m,1H); 2.33-2.4 (m, 1H); 2.7-2.8 (m, 2H); 3.1-3.2 (m, 1H); 4.8-4.9 (m, 1H).

EXAMPLE 119



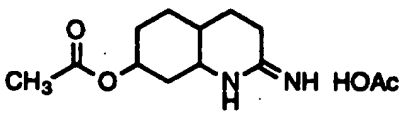
7-Hydroxy-2-imino-trans-(4a,8a)-decahydroquinoline, acetic acid salt

7-Acetyloxy-2-imino-trans-(4a,8a)-decahydroquinoline hydrochloride (28 mg, 0.12 mmol) was added to 1 mL of methanol in a 2 dram vial. The solution was cooled to 4 °C and ammonia gas was slowly bubbled in with vigorous stirring. The vial was sealed and the solution let stand at 4 °C overnight. The next morning, the solvent was removed under reduced pressure and the residue chromatographed over silica gel (17/2/1 - acetonitrile/water/acetic acid). The title compound was recovered (Rf=0.25, 7mg).

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20-1.60(m, 5H); ; 1.8-1.9(m, 2H); 1.95-2.1 (m,2H); 2.3-2.4 (m, 1H); 2.7-2.8 (m, 2H); 3.1-3.2 (m, 1H) (9β-proton); 3.6-3.8 (m, 1H).

Mass Spectrum m/e = 169 (M+1)

EXAMPLE 120



7-Acetyloxy-2-imino-decahydroquinoline, acetic acid salt

Step A: 7-Acetyloxy-octahydro-quinolin-2(1H)-one

7-Hydroxy-octahydro-quinolin-2(1H)-one, ((3/7 ratio), 250 mg, 1.48 mmol) was recovered from the mother liquors from the PtO_2 catalyzed hydrogenation of 3,4,4a,5-tetrahydroquinolin-2(1H)-7(6H)-dione (example 118 step A). This material was acetylated with acetic anhydride (2.4 mL) and 4-(dimethylamino)pyridine (40 mg) in pyridine (4.8 mL) at 0 °C. After 6 h, no starting material was seen by TLC. The solvent was removed under reduced pressure. Methylene chloride (100 mL) was added to the residue which was sequentially washed with 3x 25 mL of water, 2x 25 mL of 5% sodium bicarbonate, and 2x 25 mL of brine. After drying over $MgSO_4$, the solution was filtered and reduced in volume. Chromatography (96/4 CH_2Cl_2/MeOH) gave 160 mg of a 60/40 mixture of cis/trans isomers (by NMR).

^1H NMR (400 MHz, $CDCl_3$) δ 2.007 (s,3H) (cis acetyl); 2.013 (s,3H) (trans acetyl); 3.0 (m, 1H); 3.75 (m, 1H).

Step B: 7-Acetyloxy-2-methoxy-octahydro-quinoline

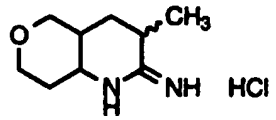
7-Acetyloxy-octahydro-quinolin-2(1H)-one (120 mg) was converted to the above compound as previously described in Step E of example 116. This product was carried on through to the amidine acetate without characterization.

Step C: 7-Acetyloxy-2-imino-decahydroquinoline, acetic acid salt

7-Acetyloxy-2-methoxy-octahydro-quinoline was converted to the title compound as prevously described in step F of example 116.

Mass Spectrum m/e = 211(M+1).

EXAMPLE 121



2-Imino-3-Methyl-octahydro-cis-pyrano[4,3-b]-pyridine hydrochloride

Step A: Benzyl-(tetrahydro-pyran-4-ylidene)-amine

A solution of tetrahydro-(4H)-pyran-4-one (10 g, 100 mmol), benzylamine (10.7 g, 100 mmol), and 50 mL of toluene was heated to reflux with a Dean-Stark trap under N_2 for 20 h. The mixture was cooled and the solvent removed under reduced pressure. The residue was distilled under reduced pressure (105-107°, 0.09mm Hg) and 5.6 g of product was isolated, yield=30%. The bulk of the reaction mixture polymerized during distillation.

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.5 (q,4H, J=8 Hz); 3.73-3.83 (t, 2H, J=8Hz); 3.85-3.95 (t, 2H, J=8Hz); 4.58 (s,2H); 7.2-7.4 (m, 5H).

Step B: 1-Benzyl-3-methyl-1,3,4,5,7,8-hexahydro-pyrano[4,3-b]pyridin-2-one

To a solution of benzyl-(tetrahydro-pyran-4-ylidene)-amine, (950 mg, 5 mmol) in a glass wall pyrolysis tube was added methyl methacrylate (750 mg, 7.5mmol, 1.5 equiv). This mixture was heated for 5 days. Then another 1.5 g of methyl methacylate was added (15 mmol, 2 equiv) and heating continued for 4 more days. The mixture was transferred to a round bottomed flask and the volatile component removed under reduced pressure. The residue was chromatographed (80/20 hexane/ethylacetate) and a lower Rf spot (530 mg, UV active on fluorescent treated silica gel plate) was isolated.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25(d,3H, J=7 Hz); 1.9-2.0 (m, 1H); 2.1-2.17(m, 2H); 2.1-2.17(m, 1H); 2.6-2.7 (m, 1H); 3.68-3.75 (m, 1H); 3.75-

3.83 (m, 1H); 4.06 (q, 2H, J=14 Hz); 4.72 (d,1H, J=16 hZ); 4.92 (d,1H, J=16 Hz); 7.12 (d, 1H, J=7 Hz); 7.20 (t, 1H, J=7 Hz); 7.25-7.29 (m, 3H).

Step C: 1-Benzyl-3-methyl-octahydro-cis-pyrano[4,3-b]pyridin-2-one

1-Benzyl-3-methyl-1,3,4,5,7,8-hexahydro-pyrano[4,3-b]pyridin-2-one (570 mg, 22.2 mmol) was dissoved in ethanol (10 mL) and placed in a small Parr pressure flask containing 270 mg of 5% rhodium/Al_2O_3. This mixture was pressurized to 60 psi and shaken for 20 h. The catalyst was filtered and the filtrate reduced in volume. Three separate spots were observed by TLC (65/35 hexane/ EtOAc). The UV active derivative was isolated by flash chromatography (90 mg) and shown to be the desired product by NMR.

^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (d,3H, J=7 Hz); 1.7-1.8 (m, 1H); 1.82-1.95 (m, 2H); 2.08(q, 1H, J=13 Hz); 2.45.2.55 (m, 1H); 3.24 (dt, 1H, J=16 Hz, J=2 Hz); 3.3-3.4 (m, 1H); 3.48(dd, 1H, J=16 Hz, J=2 Hz); 3.77 (d,1H, J=12 Hz); 3.926 (d,1H, J=15 Hz); 3.90 (m, 1H); 5.27 (d, 1H, J=15 Hz); 7.2-7.35 (m, 5H).

Step D: 3-Methyl-octahydro-cis-pyrano[4,3-b]pyridin-2-one

1-Benzyl-3-methyl-octahydro-cis-pyrano[4,3-b]pyridin-2-one (90 mg, 0.35 mmoL) was placed in a 25 mL 3-neck flask fitted with a Teflon stirrer bar, gas inlet valve and a dry ice condenser. The flask was flushed with N_2 and ammonia was condensed into the flask (15 mL). Then sodium metal was added portionwise into the solution until a blue color just persisted (~25 mg). After 1 h, 30 mg of ammonium chloride was added. The ammonia gas was allowed to evaporate, 3 mL of water was added and the resultant solution extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and the residue chomatographed on silica gel (98/2 CH_2Cl_2/MeOH) to recover 22 mg of product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (d,3H, J=10 Hz); 1.7-1.85 (m, 4H); 2.0-2.1(m, 1H); 2.35.2.45 (m, 1H); 3.35-3.4 (m, 1H); 3.5-3.6(m, 1H); 3.62 (dd,1H, J=12 Hz, J=3 Hz); 3.77(d,1H, J=12 Hz); 3.75-3.80 (m, 1H).

Step E: 2-Methoxy-3-methyl-hexahydro-cis (4*H*)pyrano[4,3-*b*]pyridine

3-Methyl-octahydro-cis-pyrano[4,3-b]pyridin-2-one (22 mg, 0.14 mmol) was converted to the imino ether by the method as previously described in step E of example 116 to recover 20 mg of product.

^{1}H NMR 200 MHz($CDCl_3$) δ 1.14(d,3H, J=7 Hz); 1.3-1.5 (m, 1H); 1.6-1.9 (m, 5H); 2.2-2.4(m, 1H); 3.37 (dt, 1H, J=12 Hz, J=2 Hz); 3.5-3.62 (m, 1H); 3.61 (s, 3H); 3.6-3.7(m, 1H); 3.8-3.9 (m, 1H).

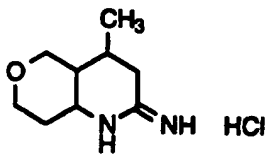
Step F: 2-Imino-3-Methyl-octahydro-cis-pyrano[4,3-*b*]-pyridine hydrochloride

2-Methoxy-3-methyl-hexahydro-cis (4H)pyrano[4,3-b]pyridine (20 mg, 0.1 mmol) was converted to the above compound as prevously described in step F of example 116.

^{1}H NMR (400 MHz, CD_3OD) δ 1.18-1.25 (m, 1H); 1.36 (d,3H, J=7 Hz); 1.7-1.9(m, 4H); 2.0-2.1 (m, 1H); 2.8-2.9(m, 1H); 3.425 (dt, 1H, J=12 Hz, J=3 Hz); 3.65-3.7 (m, 1H); 3.6-3.7(m, 1H); 3.7-3.8 (m, 2H); 3.9 (m, 1H).

Mass Spectrum (M+1)=191.

EXAMPLE 122



2-Imino-4-methyl-octahydro-pyrano*[4,3-b]*pyridine hydrochloride

Step A: 1-Benzyl-4-methyl-1,3,4,5,7,8-hexahydro-pyrano*[4,3-b]*pyridin-2-one

To a solution of benzyl-(tetrahydro-pyran-4-ylidene)-amine, (5.0g, 26 mmol) in a glass wall pyrolysis tube was added methyl crotonate (40g, 260 mmol, 10equiv) and heated for 7 days. The mixture was transfered to a round bottomed flask and the volatile component removed under reduced pressure. The mixture was chromatographed (75/25 hexane/ethylacetate) to give three spots. The hightest Rf material was the Michael addition adduct of benzyl amine to methyl crotonate. The next lower Rf spot is 4-methyl-1,3,4,4α,5,7-hexahydro-pyrano*[4,3-b]*pyridin-2-ylidene-amine, the 8,8a unsaturated analog of the bicyclic pyran while the lowest Rf product is the desired intermediate (900 mg, 3.5 mmol)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (d,3H, J=6 Hz); 2.1-2.2 (m, 1H); 2.25-2.35(m, 3H); 2.70 (dd,1H, J=12 Hz, J=6 Hz); 3.65-3.70 (m, 1H); 3.75-3.85 (m, 1H); 4.10 (q, 2H, J=14 Hz); 4.65 (d,1H, J=16 Hz); 5.01 (d,1H, J=16 Hz); 7.1-7.3 (m, 5H).

Step B: 4-Methyl-1,3,4,5,7,8-hexahydro-pyrano*[4,3-b]*pyridin-2-one

1-Benzyl-4-methyl-1,3,4,5,7,8-hexahydro-pyrano*[4,3-b]*pyridin-2-one (800 mg, 3.2 mmol) was debenzylated according to the the method of example 121, step D to recover 190 mg of product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (d,3H, J=6 Hz); 2.14 (m, 2H); 2.27-2.35(m, 2H); 2.61 (dd,1H, J=12 Hz, J=6 Hz); 3.81(t, 2H, J=9 Hz); 4.10 (q, 2H, J=14 hZ).

Step C: 4-Methyl-octahydro-cis-pyrano*[4,3-b]*pyridin-2-one

4-Methyl-1,3,4,5,7,8-hexahydro-pyrano[4,3-b]pyridin-2-one (210 mg, 1.25 mmol) was hydrogenated using 5% rhodium on alumina as prevously described in example 121 step C for 1-benzyl-3-methyl-octahydro-cis-pyrano[4,3-b]pyridin-2-one. Recovered 61 mg of product. The NMR indicated approximately a 9/1 ratio of the β/α 4-methyl product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d,3H, J=6 Hz); 1.53 (d, 1H, J=18 Hz); 1.95-2.1 (m, 4H); 2.34 (dd,1H, J=18 Hz, J=6 Hz); 3.44 (t, 1H, J=12 Hz); 3.53 (t, 1H, J=12 Hz); 3.7-3.78 (m, 2H); 3.80 (dd, 1H, J=12 Hz, J=5 Hz); 6.35 (bs, 1H).

Step D: 2-Methoxy-4-methyl-hexahydro-cis, trans(4H)pyrano[4,3-b]pyridine

4-Methyl-octahydro-cis-pyrano[4,3-b]pyridin-2-one (60 mg, 0.35 mmoL) was converted to the above compound as previously described in step E of example 116 for 2-methoxy-hexahydro-quinolin-7(8H)-one-7-ethyleneketal. A mixture of cis and trans ring junction derivatives was isolated. (20 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, 3H, J=7 Hz); 1.01 (d, 3H, J=7 Hz); 1.36 (d,3H, J=7 Hz); 3.69 (s, 3H); 3.74 (s, 3H).

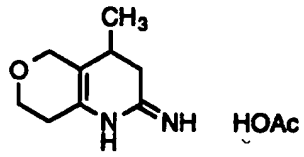
Step E: 2-Imino-4-methyl-octahydro-pyrano*[4,3-b]*pyridine hydrochloride

2-Methoxy-α,β-4-methyl-hexahydro-cis,trans(4H)pyrano- [4,3-b]pyridine (20mg) was converted to the above compound as prevously described in example 116,step F.

^{1}H NMR (400 MHz, CD_3OD) δ 1.09(d, 3H, J=7 Hz); 1.03 (d,3H, J=7 Hz).

Mass Spectrum m/e = 168.(M+1)

EXAMPLE 123



2-Imino-4-Methyl-1,3,4,5,7,8-hexahydro-pyrano[*4,3-b*]pyridine, acetic acid salt

Step A: 2-Methoxy-4-methyl-3,5,7,8-tetrahydro-4H-pyrano[4,3-b]pyridine

4-Methyl-1,3,4,5,7,8-hexahydro-pyrano[4,3-b]pyridin-2-one (42 mg, 0.25 mmoL), obtained in step A example122, was converted to the above compound as previously described in example 116 step E.

^{1}H NMR 400 MHz($CDCl_3$) δ 0.92 (d,3H, J=7 Hz); 2.1-2.15 (m, 2H); 2.2-2.6(m, 3H); 3.30 (d,1H, J=12 Hz); 3.80(s, 3H); 4.05-4.2(q, 2H, J=16 hZ).

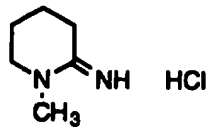
Step B: 2-Imino-4-Methyl-1,3,4,5,7,8-hexahydro-pyrano[*4,3-b*]pyridine, acetic acid salt

2-Methoxy-4-methyl-3,5,7,8-tetrahydro-4H-pyrano[4,3-b]pyridine (16 mg, 0.1 mmoL) was converted to the above compound as prevously described in example 116 step F.

^{1}H NMR (400 MHz, CD_3OD) δ 1.044(d, 3H, J=7Hz); 1.93 (s, 3H, acetate protons); 2.2-2.3 (m, 2H); 2.4-2.47 (m, 1H); 2.56 (dd, 1H, J=12 Hz, J=6 Hz); 3.94 (dd,1H, L=16 Hz, J=5 Hz); 3.33(dd, 1H, J=9 Hz, J=2Hz); 3.84 (t 1H, J=5 Hz); 4.1-4.23(m, 1H).

Mass Spectrum m/e =167.(M+1)

EXAMPLE 124



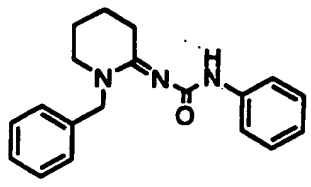
2-Imino-1-methyl-piperidine hydrochloride

This compound was prepared according to the procedure described by Rama Rao *et al.*in *Syn. Comm.*: **18**, 877-880 (1988).

^{1}H NMR (400 MHz, CD_3OD): δ 1.89 (m, 4H); 2.62 (t, 2H); 3.14 (s, 3H); 3.53 (t, 2H).

Mass spectrum m/e = 114 (M+1)

EXAMPLE 125



N-(1-Benzyl-2-piperidinylidene)-N'-(phenyl)-urea

Step A: 2-Imino-1-benzyl-piperidine tetrafluoroborate

To a solution N-benzyl-valerolactam (1.3 g, 6.87 mmol) in methylene chloride (25 mL) was added trimethyloxonium

tetrafluoroborate (1.12 g, 7.57 mmol). The reaction mixture was stirred overnight at room temperature under a nitrogen atmosphere. Dry ammonia gas was then bubbled through the reaction mixture for one hour, and the mixture was allowed to stand for an additional hour at room temperature. The mixture was evaporated under diminished pressure and dried *in vacuo*. The crude product was used without further purification in Step B.

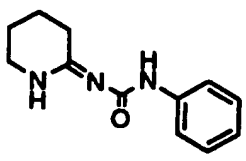
Step B: N-(1-Benzyl-2-piperidinylidene)-N'-(phenyl)-urea

The fluoboric acid salt from Step A was treated with several mL's of 50% sodium hydroxide, and the free 2-imino-1-benzyl-piperidine was extracted with benzene. The benzene layer was decanted, dried (K_2CO_3), and evaporated to give an oil. 300 mg of the resulting oil was dissolved in methylene chloride (2.5 mL) and treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (204 µL, 1.36 mmol) and phenyl isocyanate (148 µL, 1.36 mmol). The reaction mixture was stirred overnight at room temperature, diluted with methylene chloride, washed with 2 N hydrochloric acid, saturated sodium hydrogencarbonate solution, saturated brine solution, dried (Na_2SO_4), and evaporated. The product was crystallized from ethyl acetate; yield 150 mg.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.76 (m, 4H); 3.04 (t, 2H); 3.25 (t, 2H); 4.78 (s, 2H); 6.93-7.34 (m, 10H).

Mass spectrum m/e = 308 (M +1).

EXAMPLE 126



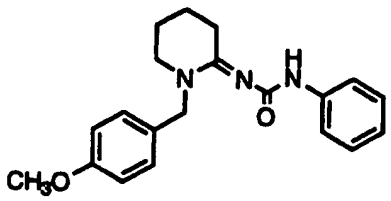
N-(2-Piperidinylidene)-N'-(phenyl)-urea

N-(1-Benzyl-2-piperidinylidene)-N'-(phenyl)-urea (70 mg, 0.228 mmol, from Example 125) in glacial acetic acid (2 mL) was hydrogenolyzed in the presence of 10% Pd/C (30 mg) for 8 h. The catalyst was removed by filtration through an Anotop 25 Dispo Syringe Filter (0.2 μm). The filtrate was evaporated and coevaporated several times with toluene. The product was purified by flash silica gel chromatography eluting with 1-5% methanol/CH_2Cl_2; yield 15 mg.

^1H NMR (400 MHz, CD_3OD): δ 1.85 (m, 4H); 2.59 (br m, 2H); 3.50 (br m, 2H); 7.05 (t, 1H); 7.28 (t, 2H); 7.50 (d, 2H).

Mass spectrum m/e = 218 (M +1).

EXAMPLE 127



N-[1-(4-Methoxybenzyl)-2-piperidinylidene]-N'-(phenyl)-urea

Step A: 2-Imino-1-(4-methoxybenzyl)-piperidine tetrafluoroborate

This compound was prepared in a similar manner as in Step A of Example 126. The crude product was used without further purification in Step B.

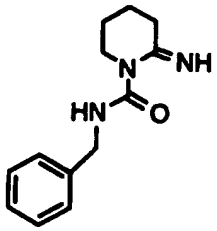
Step B: N-[1-(4-Methoxybenzyl)-2-piperidinylidene]-N'-(phenyl)-urea

The fluoboric acid salt from Step A was treated with several mL's of 50% sodium hydroxide, and the free 2-imino-1-(4-methoxybenzyl)-piperidine was extracted with benzene. The benzene layer was decanted, dried (K_2CO_3), and evaporated to give an oil. 300 mg of the resulting oil was dissolved in methylene chloride (2 mL) and treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (204 µL, 1.36 mmol) and phenyl isocyanate (148 µL, 1.36 mmol). The reaction mixture was stirred for 2 hours at room temperature, diluted with methylene chloride, washed with 2 N hydrochloric acid, saturated sodium hydrogencarbonate solution, saturated brine solution, dried (Na_2SO_4), and evaporated. The product was purified by flash silica gel chromatography eluting with 30% ethyl acetate in hexane; yield 127 mg.

^1H NMR (400 MHz, $CDCl_3$): δ 1.73 (m, 4H); 3.03 (t, 2H); 3.22 (t, 2H); 3.79 (s, 3H) 4.70 (s, 2H); 6.83-7.27 (m, 9H).

Mass spectrum m/e = 338 (M +1).

EXAMPLE 128



2-Imino-1-(benzylaminocarbonyl)-piperidine

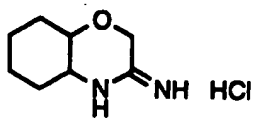
To a mixture of 2-imino-piperidine hydrochloride (250 mg, 1.86 mmol) in acetonitrile (8 mL) cooled in an ice-bath were added 1,8-diazabicyclo[5.4.0]undec-7-ene (277 µL, 1.85 mmol) and benzyl isocyanate (229 µL, 1.85 mmol). The reaction mixture was stirred overnight at room temperature and then evaporated. The product was

purified by flash silica gel chromatography eluting with 2-3% methanol/CH_2Cl_2.

^1H NMR (400 MHz, CD_3OD): δ 1.78 (m, 4H) 2.37 (m, 2H); 3.39 (m, 2H); 4.34 (s, 2H); 7.18-7.31 (m, 5H).

Mass spectrum m/e = 232 (M + 1).

EXAMPLE 129



Cis-Octahydro-3-imino-2H-1,4-benzoxazine hydrochloride:

Step A: Cis-hexahydro-1,4-benzoxazin-3(4H)-one:

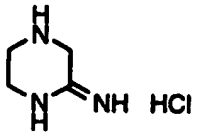
A mixture of 2H-1,4-benzoxazin-3(4H)-one (1g) and platinum oxide (0.5g) in 50 mL of glacial acetic acid was hydrogenated on Parr shaker at room temperature and 50 psi for 2 days. The catatlyst was filtered and washed with acetic acid. The filtrate was concentrated to give the desired lactam as white solid after purification on silica gel using 2% methanol in ethyl acetate as solvent.

Step B: Cis-Octahydro-3-imino-2H-1,4-benzoxazine hydrochloride

The title compouhd was prepared according to the method described in Examples 2 and 3.

^1H NMR (D6-DMSO): 4.52(m,2H); 3.88(m,1H); 1.16-1.8(m,8H)

EXAMPLE 130



2-Iminopiperazine hydrochloride

Step A: 2-Ketopiperazine

A solution of 10.2 g (81 mmol) of ethyl chloroacetate in 50 mL of ethanol was added dropwise over 1 hr to a solution of 30 g (0.5 M) of ethylene diamine in 125 mL of ethanol at room temperature. The mixture was stirred 3 hrs and 4.4 g (81 mmol) of sodium methoxide was added and the mixture was stirred additional 4 hours. The resulting voluminous white precipitate was filtered and the filtrate was concentrated to give oily residue which was heated at 200 °C (bath temperature) for 5 mins with a wide distillation head. A solid deposited in the distillation head during the distillation. After 1.5 hrs of distillation, distillation head was washed with methanol to remove the desired product. Methanol washes were concentrated to give a crude product which was purified on silica gel using 5:2 mixture of chloroform:methanol as solvent to provide 2.3 g of the desired product as yellow solid.

^{1}H NMR (DMSO): 2.74(m,2H); 3.1(m,2H); 3.13(s,2H); 7.58(b,1H)

Step B: 4-t-Butoxycarbonyl-2-ketopiperazine

A mixture of 500 mg (5 mmol) of 2-ketopiperazine, 1.2 g (5.5 mmol) of t-butyldicarbonate and 2 g of sodium chloride in 7.5 mL of water and 10 mL of chloroform was heated to reflux 4 hrs. The reaction mixture was cooled to room temperature and extracted with ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous magnesium sulfate . Solvent removal gave a crude product which was

purified on silica gel using 5% methanol in ethyl acetate as solvent to give 925 mg of the desired carbamate lactam as white solid.

^{1}H NMR ($CDCl_3$): 1.46(s,9H); 3.37(m,2H); 3.62(m,2H); 4.08(s,2H)

Step C: 4-t-Butoxycarbonyl-2-imino piperazine hydrochloride

The title compouind was prepared according to the procedure described in Examples 2 and 3.

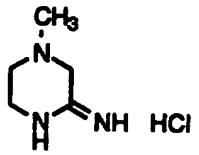
^{1}H NMR (DMSO): 1.42(s,9H); 3.35(m,2H); 3.52(m,2H); 4.32(s,2H); 8.75(b,1H); 9.04(b,1H); 10.05(b,1H).

Step D: 2-Imino piperazine hydrochloride

Hydrogen chloride gas was bubbled through 6 mL of ethyl acetate at 0 °C for 3 mins. Solid 4-t-butoxycarbonyl-2-imino piperazine hydrochloride (36 mg) was added and the mixture was stirred overnight at room temperature. Solvent and hydrochloric acid gas were evaporated in vacuo to give 24 mg of the desired imino piperazine hydrochloride as white solid.

^{1}H NMR (DMSO): 3.35(3H); 3.54(m,2H); 4.12(s,2H); 8.98(b,1H); 9.3(b,1H); 10.16(b,1H)

EXAMPLE 131



4-Methyl-2-iminopiperazine hydrochloride

Step A: 4-Methyl-2-oxo-piperazine hydrochloride:

4.4 g (100 mmol) of ethyleneimine was added to 7.8 g (66 mmol) of sarcosine ethyl ester with stirring at 60 °C. The mixture was then heated 1 day at the same temperature. Volatile materials were removed in vacuo and the residue was purified on silica gel using methanol/ethyl acetate gradient mixtures to give the title compound.

^{1}H NMR ($CDCl_3$): 3.35(2H); 3.06(2H); 2.58(2H); 2.32(3H)

The hydrochloride salt was prepared by adding ethereal hydrochloride solution to a solution of the above tertiary amine and stirring the mixture for 1 hour. The resulting solid was filtered and washed with ether and dried.

Step B: 4-Methyl-2-methoxy-3,4,5,6-tetrahydro pyrazine

A mixture of 1.505 g (10mM) of 4-methyl-2-oxo-piperazine hydrochloride from step A and 3.0 g (20 mM) of trimethyloxonium tetrafluoroborate in 150 mL of chloroform was stirred for 4 days at room temperature under nitrogen. Excess saturated sodium bicarbonate was added and stirred 30 mins. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate. After filtration the solvent was removed to give a mixture of the title compound and 4-methyl-piperazin-2-one as an oil.

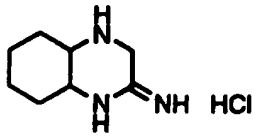
^{1}H NMR ($CDCl_3$): 3.64(s,3H); 3.36 and 3.56(4:11)(m,2H); 3.08 and 2.9 (4:11)(s,2H); 2.6 and 2.4 (4:11)(m,2H); 2.33 and 2.3(6:16.5)(s,3H)

Step C: 4-Methyl-2-iminopiperazine hydrochloride and 4-Methyl-2-oxo-piperazine hydrochloride:

This compound was prepared from 4-methyl-2-methoxy-3,4,5,6-tetrahydro pyrazine according to the procedure of example 3. This product was contained some 4-methyl-piperazin-2-one which was present in the starting material.

^{1}H NMR (CD3OD): 2.92 and 2.43 (s,3H); 3.8 and 3.42(s,2H); 2.75 and 3.56(t, 2H); 3.45 and 3.8(t,2H)

EXAMPLE 132



2-Imino-decahydro-*cis*-quinoxaline dihydrochloride

Step A: Decahydro-2(1H)-quinxalinone

To a solution of 2.28 g (20 mmol) of cis-1,2-diaminocyclohexane in 100 mL of water, 1.74 g (30 mmol) of glyoxal was added. After stirring for 4 h the reaction mixture was filtered and the filtrate was concentrated in vacuo. The residual oil was absorbed on a flash column and the column was eluted with 50% EtOAc/hexane, 10% MeOH/EtOAc and 50% MeOH/EtOAc to isolate 1.19 g of the title compound as an oil.

Step B: 4-t-Butyloxycarbonyl-decahydro-2(1H)-quinoxalinone

A solution of 1.19 g (7.72 mmol) of decahydro-2(1H)-quinxalinone in 10 mL of saturated NaHCO3 was treated with 2.2 g (10 mmol) of di-tert-butyl dicarbonate. After stirring for 2 h the reaction mixture was extracted with EtOAc and the EtOAc layer was washed with

brine and dried. The filtrate was concentrated and the residue was purified on a flash column to isolate 0.667 g of the title compound.

Step C: 4-t-Butyloxycarbonyl-2-methoxy-3,4,5,6,7,8,5a,8,a-octahydro-quinoxalinone.

To a solution of 0.254 g (1 mmol) of 4-t-butyloxycarbonyl-decahydro-2(1H)-quinoxalinone in 3 mL of CH2Cl2 was added 0.191 g (1.3 mmol) of trimethyloxonium tetrafluoroborate and the mixture was stirred overnight. The reaction mixture was partitioned between saturated NaHCO3 and CH2Cl2. The organic layer was washed with water, brine dried and concentrated. The residue was chromatographed using 20% Et2O-hexane as an eluent to isolate 0.124 g of the title compound.

Step D: 4-t-Butoxy-2-imino-decahydro-cis-quinoxaline

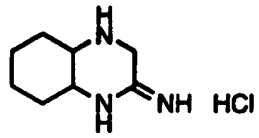
A solution of 0.123 g (0.45 mmol) of 4-t-Butyloxycarbonyl-2-methoxy-3,4,5,6,7,8,5a,8,a-octahydro-quinoxalinone in 3 mL of EtOH containing 22 mg (0.41 mmol) of NH4Cl was heated to reflux. After 3 h at reflux the reaction mixture was concentrated, the residue was triturated with Et2O and the solid was filtered and dried to isolate 0.055 mg of the title compound.

Step E: 2-Imino-decahydro-cis-quinoxaline

To 46 mg of 4-t-butoxy-2-imino-decahydro-cis-quinoxaline 3 mL of EtOAc saturated with HCl was added. The reaction turned clear momentarily and another solid was formed. After 30 min the solid was filtered washed with Et2O and dried to furnish 32 mg of the title compound.

^{1}H NMR (D2O): 1.50 (br s, 3H), 1.66 (br s, 1H), 1.89 (br s, 4H), 3.92 (m, 1H), 4.0 (m, 1H), 4.37 (s, 2H)

EXAMPLE 133

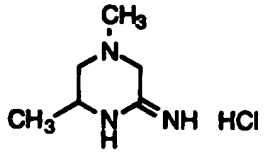


2-Imino-decahydro-*trans*-quinoxaline dihydrochloride

The title compound was prepared by the procedure of example 132 starting with trans-1,2-diaminocyclohexane.

^{1}H NMR (D2O): 1.3-1.6 (m,4H), 1.8-1.9 (m, 2H), 2.16 (t, 2H), 3.3 (td, 1H, J = 11 and 4 Hz), 3.55 (td, 1H, J = 11 and 4 Hz), 4.41 (ABq, 2H)

EXAMPLE 134



4-6-Dimethyl-2-imino-piperazine hydrochloride

Step A: 4,6-Dimethyl-2-keto-piperazine

A solution of 0.8 mL (10.2 mmol) 2-methylaziridine (90%), 0.998 g (11.21 mmol) of sarcosine and 30 mg of NH_4Cl in 4 mL of water was heated to 100 °C in a sealed tube for 2 h. The mixture was allowed to stand overnight, then concentrated in vacuo. The residue was purified by chromatography using 30% MeOH-EtOAc to yield 0.637 g (49%) of the desired product.

^{1}H NMR (CDCl3): 1.13 (d, 3H), 2.03 (m, 1H), 2.28 (s, 3H), 2.77 (m, 2H), 3.23 (d, 1H), 3.62 (br s, 1H), 6.8 (br s, 1H).

Step B: 4,6-Dimethyl-piperazin-2-thione

To a solution of 1.011 g (5.09 mmol) of 4,6-dimethyl-2-keto-piperazine in 25 mL of dioxane, 4.704 g (56 mmol) of $NaHCO_3$ and 1.56 g (3.56 mmol) of phosphorus pentasulfide were added and the mixture was heated in a 70 °C bath. After 6 h the reaction was cooled, quenched by adding water (gas evolution) and stirred overnight. The solution was extracted with EtOAc. The EtOAc layer was washed with brine, dried and concentrated. The residue was chromatographed using a gradient of 0-10% MeOH/EtOAc to isolate 91 mg of the desired product.

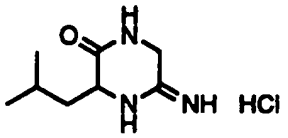
Step C: 4-6-Dimethyl-2-imino-piperazine hydrochloride

Ammonia gas passed through a THF (5 mL) solution of 72 mg (0.499 mmol) of 4,6-dimethyl-piperazin-2-thione kept in a 50 °C bath for 5 min. To this solution 149 mg (0.55 mmol) of $HgCl_2$ was added and the reaction was heated to 50 °C for 15 min after it turned black. The solution was filtered through a pad of celite and the pad was rinsed with MeOH. The combined filtrate was concentrated and the residue was purified on a flash column using MeCN followed by 70:2:1 mixture of MeCN:H2O:HOAC to isolate 30 mg of the title compound.

^{1}H NMR (CD3OD): 1.25 (d, 3H), 1.9 (s, 3H), 2.27 (dd, 1H), 2.9 (dd, 1H), 3.22 (d, 1H), 3.45 (d, 1H), 3.72 (m, 1H).

Mass spectrum m/e = 127

EXAMPLE 135



2-Imino-4-methyl-6-(2-methylpropyl)-5-oxo-piperazine hydrochloride

Step A: N-t-Butyloxycarbonylglycinylsarcosine ethyl ester

To a solution of 0.629 g (3.59 mmol) of t-butoxycarbonyoxyglycine in 8 mL of CH_2Cl_2 0.58 g (4.31 mmol) of hydroxybenztriazole,0.87 mL (7.9 mmol) of N-methylmorpholine and 0.826 g (4.31 mmol) of EDAC were added. After 10 min 0.607 g (3.95 mmol) of sarcosine ethyl ester hydrochloride was added and the mixture was stirred overnight. The reaction was poured into water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried and the filtrate was concentrated. The residue was purified on a flash column eluting with 50% EtOAc-hexane to obtain 0.985 (96%) of N-t-butyloxycarbonylglycinylsarcosine ethyl ester.

Step B: 1-Methyl-2,5-diketopiperazine

A solution of 0.942 g (3.43 mmol) of N-t-butyloxycarbonylglycinylsarcosine ethyl ester in 10 mL of EtOAc was saturated with HCl gas. After stirring for 1 h the solution was concentrated in vacuo to leave a white solid. The solid was dissolved in 10 mL of EtOH, 0.474 g (3.43 mmol) of powdered K_2CO_3 was added and the mixture was heated in a 60 °C bath overnight. The solid was filtered and rinsed with EtOH and the combined filtrate was concentrated to leave a solid. The solid was washed with ether and dried to furnish 0.499 g of the title compound.

^1H NMR (CDCl3): 2.98 (s, 3H), 3.97 (s, 2H), 4.02 (s, 2H), 6.23 (br s, 1H).

Step C: 2-Methoxy-4-methyl-3,4-dihydro-5(6H)-pyrazinone.

Treatment of 1-methyl-2,5-diketopiperazine with trimethyloxonium tetrafluoroborate as described in example 132 step C gave the title compound.

Step D: 2-Methoxy-4-methyl-6-(2-methylpropyl)-3,4-dihydro-5(6H)-pyrazinone.

To a solution of 0.171 g (1.2 mmol) of 2-methoxy-4-methyl-3,4-dihydro-5(6H)-pyrazinone in 6 mL of THF cooled in a -78 °C bath, 0.72 mL (2M in THF, 1.44 mmol) of LDA was added. After 10 min 0.17 mL (1.56 mmol) of 1-bromo-2-methylpropane was added and the solution was allowed to warm to room temperature over the next 2 h. After stirring for 0.5 h the reaction was quenched by adding water and the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried and the filtrate was concentrated. The residue was purified on a flash column using a gradient of 30-50% EtOAc-hexane to isolate 0.1 g (42%) of the title compound.

^{1}H NMR (CDCl3): 0.91 (d, 3H), 0.94 (d, 3H), 1.4-1.9 (m, 3H), 2.93 (s, 3H), 3.69 (s, 3H), 3.81 and 3.94 (ABq, 2H), 4.09 (m, 1H).

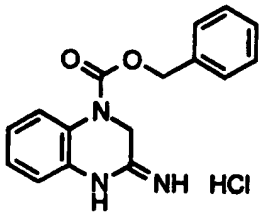
Step E: 2-Imino-4-methyl-6-(2-methylpropyl)-5-oxo-piperazine

A solution of 0.1 g of 2-methoxy-4-methyl-6-(2-methylpropyl)-3,4-dihydro-5(6H)-pyrazinone in 1 mL of EtOH was reacted with NH4Cl as described in example 132 step D to furnish the title compound.

^{1}H NMR (CD3OD): 0.96 (d, 6H), 1.6-1.9 (m, 3H), 3.0 (s, 3H), 4.11 (t, 1H), 4.47 and 4.61 (AB q, 2H).

Mass spectrum m/e = 184 (M+1)

EXAMPLE 136



4-Benzyloxycarbonyl-2-imino-(1,2,3,4)tetrahydro-quinoxaline hydrochloride

Step A: 3,4-Dihydo-2(1H)-quinaxolone

To a solution of 1.2 g (8.2 mmol) of 2-hydroxyquinoxaline in 10 mL of EtOH, 220 mg of PtO_2 was added and the solution was hydrogenated on a Parr apparatus overnight. The catalyst was filtered and washed with EtOH and the filtrate was concentrated to yield 1.17 g (96%) of the title compound sufficiently pure for use without purification.

^1H NMR (CDCl3): 3.97 (s, 2H), 6.6-6.9 (m, 4H), 8.1 (br s, 1H).

Step B: 4-Benzyloxycarbonyl-3,4-dihydro-2(1H)-quinaxolone

A solution of o.41 g (2.77 mmol) of 3,4-dihydo-2(1H)-quinaxolone in 5 mL of CH2Cl2 and 5 mL of saturated $NaHCO_3$ was treated with 0.44 mL (3.05 mmol) of benzylchloroformate. After stirring for 4 h, the reaction was diluted with CH_2Cl_2, washed with water, brine and dried. The filtrate was concentrated and the residue was chromatographed using 30% EtOAc-hexane to isolate 0.31 g of the desired product.

^{1}H NMR (CDCl3): 4.44 and 4.58 (2s, 2H), 5.24 and 5.28 (2s, 2H), 6.8-7.4 (m, 9H).

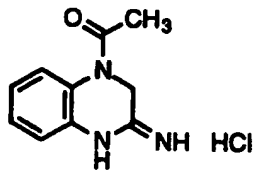
Step C: 4-Benzyloxycarbonyl-2-imino-(1,2,3,4)tetrahydro-quinoxaline hydrochloride

The 4-benzyloxycarbonyl-3,4-dihydro-2(1H)-quinaxolone obtained in step B was subjected to the reactions described in example 134 steps B and C furnished the title compound.

^{1}H NMR (CD3OD): 4.31 (s, 2H), 5.23 (s, 2H), 6.9-7.5 (m, 9H).

Mass spectrum m/e = 282 (M+1)

Example 137



4-Acetyl-2-imino-(1,2,3,4)tetrahydro-quinoxaline hydrochloride

Step A: 4-Acetyll-3,4-dihydro-2(1H)-quinaxolone

A solution of 0.212 g (1.43 mmol) of 3,4-dihydo-2(1H)-quinaxolone (example 136, step A) in 7 mL of CH_2Cl_2 was treated with 0.12 mL (1.72 mmol) of acetyl chloride and 0.26 mL (1.86 mmol) of Et_3N. After 2 h another 0.04 mL of acetyl chloride was added to complete the reaction and the solution was partitioned between water and CH2Cl2. The CH_2Cl_2 layer was washed with brine, dried and concentrated. The residue was purified by chromatography.

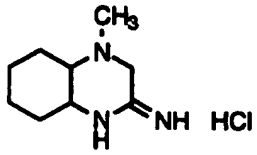
Step B: 4-Acetyl-2-imino-(1,2,3,4)tetrahydro-quinoxaline

Treatement of 4-acetyll-1,2,3,4-tetrahydro-2-quinaxolone by the method of example 134 steps B and C furnished the title compound.

^{1}H NMR (CD3OD): 2.24 (s, 3H), 4.5 (s, 2H), 7.0-7.5 (m, 4H).

Mass spectrum m/e = 189 (M+1)

EXAMPLE 138



2-Imino-4-methyl-decahydro-*trans*-quinoxaline, acetic acid salt

Step A: 4-methyl-octahydro-trans-2(1H)-quinoxalone

To 0.537 g of 4-t-butyloxycarbonyl-octahydro-trans-2(1H)-quinoxalone (Example 133), 10 mL of EtOAc saturated with HCl gas was added. After stirring for 2 h the solvent was removed in vacuo to give 0.483 g of a brown solid.

To a solution of 0.147 g (0.77 mmol) of this solid in 5 mL of MeOH and 1 mL of formaldehyde (37% aq. solution) was added 50 mg of 10 % Pd/C and the mixture was hydrogenated under 41 psi for 3 h. The catalyst was filtered through a pad of celite and the pad washed with MeOH and the filtrate was concentrated to yield 0.325 g of the title compound.

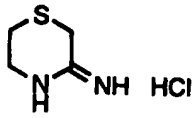
Step B: 2-Imino-4-methyl-decahydro-trans-quinoxaline, acetic acid salt

The product of step A was reacted as described in example 134 steps B and C to isolate the title compound

^{1}H NMR (CD3OD): 1.2-2.2 (m, 9H), 1.92 (s, 3H), 2.31 (s, 3H), 3.18 (m, 1H), 3.31 (d, 1H), 3.70 (d, 1H).

Mass spectrum m/e = 168 (M+1)

EXAMPLE 139



3-Iminothiomorpholine hydrochloride.

Step A: Thiomorpholin-3-one

To 6.5 g (0.15 mol) of ethyleneimine was added to 12 g (0.1 mol) of ethyl thiol acetate with stirring at 60 °C. After the addition, the mixture was heated for 2.5 h at the same temperature. It was then allowed to cool to room temperature and then allowed to stand 1 day at room temperature. Robust white crystals formed. The liquid was decanted and the solid was washed with ice cold ethyl alcohol to afford 6.2 g of the desired thiomorpholinone.

^{1}H NMR ($CDCl_3$): 2.8(m,2H); 3.28(s,2H); 3.62(m,2H); 6.62(b,1H)

Step B: Thiomorpholin-3-thione

A mixture of 1.17 g (10 mmol) of thiomorpholin-3-one and 11 mmoles of Lawesson's reagent in 25 mL of toluene was heated to reflux 2 hrs. The reaction mixture was cooled and the solvent was removed to give a residue. This was taken up in methylene chloride and

applied on silica gel column and eluted with ethyl acetate containing methylene chloride (10%). The desired thiomorpholin-3-thione in 65% yield as solid.

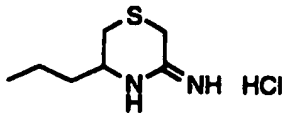
^{1}H NMR ($CDCl_3$): 2.90(m,2H); 3.62(m,2H); 3.76(s,2H); 8.65(b,1H)

Step C: 3-Imino thiomorpholine hydrochloride

The title amidine was prepared from thiomorpholin-3-thione according to the procedure of example 43 step F.

^{1}H NMR (DMSO): 2.92(m,2H); 3.52(m,2H); 3.62(s,2H); 8.85(b,1H); 9.28(b,1H); 9.9(b,1H)

EXAMPLE 140



3-Imino-5-propyl-thiomorpholine

Step A: 2-Butoxycarbonylamino-1-pentanol

To a solution of 1.1 mL (9.8 mmol) of 2-amino-1-pentanol in 10 mL of MeCN was added 2.18 g (10 mmol) of di-t-butyl dicarbonate followed by a solution of 1.06 g (10 mmol) of Na_2CO_3 in 10 mL of water. After stirring for 4 h the reaction mixture was partitioned between Et_2O:EtOAc (1:1) and water. The organic layer was washed with water, brine and dried. The filtrate was concentrated to furnish 2.8 g of a liquid which was used in the next step without purification.

^{1}H NMR (CDCl3): 0.91 (t, 3H), 1.3-1.9 (m, 11H), 2.31 (t, 2H), 2.4 (br s, 1H), 3.0 (s, 3H), 3.8 (br, 1H), 4.15 (dd, 1H, J=10 and 4 Hz), 4.22 (m, 1H), 4.57 (br, 1H).

Step B: Ethyl ((2-butoxycarbonylaminopentyl)thio)acetate

A solution of 0.7 g of 2-butoxycarbonylamino-1-pentanol prepared in step A in 5 mL of CH_2Cl_2 was treated with 0.23 mL (3 mmol) of methanesulfonyl chloride. The mixture was cooled in ice bath and 0.42 mL (3 mmol) of Et_3N was added and the solution was allowed to warm to room temperature. After 1 h another 0.05 mL (0.65 mmol) of methanesulfonyl chloride and 0.1 mL (0.71 mmol) of Et_3N were added and stirred for 15 min. the reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ solution, water, 1.2 N HCl and brine. The organic layer was dried and concentrated to yield 0.94 g of the mesylate as a white solid.

^{1}H NMR (CDCl3): 0.91 (t, 3H), 1.2-1.9 (m, 11H), 2.32 (t, 2H), 3.51 (m, 1H), 3.63 (m, 2H), 4.57 (br s, 1H).

To a solution of the mesylate in 5 mL of EtOH 0.3 mL (2.7 mmol) of ethyl 2-mercaptoacetate and 0.42 g (3 mmol) of powdered K_2CO_3 were added. The mixture was heated in a 50 °C bath for 2 h, then diluted with water and extraced with EtOAc. The EtOAc layer was washed with water, brine, dried and concentrated. The residue was chromatographed on a flash column using a gradient of 20-50% EtOAc-Hexane to isolate 0.48 g (63%) of the title compound.

^{1}H NMR (CDCl3): 0.90 (t, 3H), 1.2-2.3 (m, 16H), 2.72 (m, 2H), 3.23 (ABq, 2H), 3.75 (br, 1H), 4.19 (q,2H),4.57 (br s, 1H).

Step C: 5-Propyl-thiomorpholin-3-one

Ice cold EtOAc (5 mL) was saturated with HCl gas and this solution was added to 0.48 g (1.57 mmol) of ethyl ((2-butoxycarbonylaminopentyl)thio)acetate. After stirring for 1 h the solution was concentrated to give 0.42 g of amine hydrochloride as an oil. The oil was dissolved in 3 mL of EtOH and 0.207 g (1.5 mmol) of powdered K_2CO_3 was added. After heating the mixture in a 80 °C bath for 2.5 h the reaction was cooled and partitioned between water and EtOAc. The organic layer was washed with water, brine, dried and concentrated. The residue was purified by flash chromatography using 30-100% EtOAc-hexane to yield 0.15 g (60%) of the title compound as a white solid.

^{1}H NMR (CDCl3): 0.94 (t, 3H), 1.36 (m, 2H), 1.57 (m, 2H), 2.53 (dd, 1H, J=13 and 9 Hz), 2.78 (dd, 1H, J=13 and 4 Hz), 3.26 (ABq, 2H), 3.63 (m, 1H), 5.8 (br s, 1H).

Step D: 5-Propyl-thiomorpholin-3-thione

A solution of 0.15 g (0.94 mmol) of 5-propyl-thiomorpholin-3-one in 3 mL of toluene was treated with 0.44 g (1.1 mmol) of Lawesson's reagent and the reaction was heated to reflux. After 1 h the solution was cooled to room temperature, diluted with 2 mL of hexane and allowed to stand overnight. The solid formed was removed by filtering through a 0.5 u filter and the filtrate was concentrated. The residue was chromatographed using 10-30% EtOAc/hexane to obtain 0.131 g (80%) of the title compound.

^{1}H NMR (CDCl3): 0.95 (t, 3H), 1.41 (m, 2H), 1.64 (m, 2H), 2.60 (dd, 1H, J=13 and 9 Hz), 2.89 (dd, 1H, J=13 and 4 Hz), 3.57 (m, 1H), 3.74 (ABq, 2H, J=17Hz), 8.3 (br s, 1H).

Step F: 3-Imino-5-propyl-thiomorpholine

A solution of 0.131 g (0.75 mmol) of 5-propyl-thiomorpholin-3-thione in 3 mL of CH_2Cl_2 was stirred with 4 Å molecular sieves. After 10 min 0.125 g (0.85 mmol) of trimethyloxonium tetrafluoroborate was added and the mixture was stirred for 2.5 h. The reaction was quenched by adding saturated $NaHCO_3$ solution then extraced with CH_2Cl_2. The organic layer was washed with brine, dried and concentrated to give 0.115 g of a brown oil.

^1H NMR (CDCl3): 0.94 (t, 3H), 1.4 - 1.8 (m, 4H), 2.29 (s, 3H), 2.3 (m, 1H), 2.73 (dd, 1H, J=13 and 4 Hz), 3.12 (ABq, 2H), 3.43 (m, 1H).

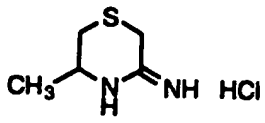
The brown oil in 1 mL of EtOH was trated with 30 mg (0.56 mmol) of NH4Cl and the mixture was heated to reflux. After 1 h the solution was concentrated and the residue was chromatographed on a flash column using a gradient of MeCN, MeCN/HOAc - 95:5, MeCN/H2O/HOAc - 90:5:5 and finally MeCN/H2O/HOAc - 85:10:5 to isolate 37 mg (23%) of the title compound as an acetic acid salt.

^1H NMR (CDCl3): 0.94 (t, 3H), 1.3 - 1.8 (m, 4H), 2.05 (s, 3H), 2.63 (dd, 1H, J=13 and 9 Hz), 2.92 (dd, 1H, J=13 and 4 Hz), 3.65 (m, 3H), 8.2 (br s, 1H).

Mass spectrum m/e = 159 (M+1)

The compounds of Examples 141-145 were prepared by the method of example 101 starting from the appropriate aminoalcohol.

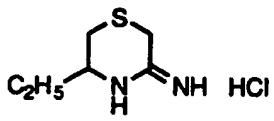
EXAMPLE 141



3-Imino-5-methyl-thiomorpholine

^{1}H NMR (CD3OD): 1.38 (d, 3H), 2.71 (dd, 1H, J=13 and 9 Hz), 3.07 (dd, 1H, J=13 and 4 Hz), 3.60 (ABq, 2H, J=16 Hz), 3.82 (m, 1H).

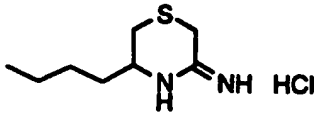
EXAMPLE 142



3-Imino-5-ethyl-thiomorpholine

^{1}H NMR (CD3OD): 1.03 (t, 3H), 1.75 (m, 2H), 2.75 (dd, 1H, J=13 and 9 Hz), 3.1 (dd, 1H, J=13 and 4 Hz), 3.6 (m, 3H).

EXAMPLE 143

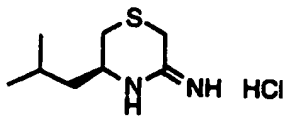


3-Imino-5-butyl-thiomorpholine

^{1}H NMR (CDCl3): 0.95 (t, 3H), 1.3 - 1.8 (m, 6H), 2.75 (dd, 1H, J=13 and 9 Hz), 3.1 (dd, 1H, J=13 and 4 Hz), 3.60 (m, 3H).

Mass spectrum m/e = 173 (M+1)

EXAMPLE 144

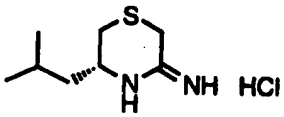


3-Imino-5(S)-(2-methyl propyl)-thiomorpholine

^{1}H NMR (CDCl3): 0.97 (d, 6H), 1.6 (m, 2H), 1.77 (m, 1H), 2.72 (dd, 1H, J=13 and 9 Hz), 3.1 (dd, 1H, J=13 and 4 Hz), 3.52 (d, 1H, J=16 Hz), 3.68 (d, 1H, J=16 Hz), 3.75 (m, 1H).

Mass spectrum m/e = 173 (M+1)

EXAMPLE 145

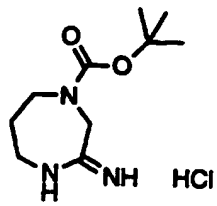


3-Imino-5(R)-(2-methyl propyl)-thiomorpholine

^{1}H NMR (CDCl3): 0.97 (d, 6H), 1.6 (m, 2H), 1.77 (m, 1H), 2.72 (dd, 1H, J=13 and 9 Hz), 3.1 (dd, 1H, J=13 and 4 Hz), 3.52 (d, 1H, J=16 Hz), 3.68 (d, 1H, J=16 Hz), 3.75 (m, 1H).

Mass spectrum m/e = 173 (M+1)

EXAMPLE 146



1-(*tert*-Butoxycarbonyl)-hexahydro-3-imino-(1*H*)-1,4-diazepine hydrochloride.

Step A: 4-(*tert*-Butoxycarbonyl)-hexahydro-(2*H*)-1,4-diazepin-2-one.

Hexahydro-(2*H*)-1,4-diazepin-2-one (300 mg, 2.63 mmol), obtained by the procedure of B. Kotelko, R. Glinka, R. Guryn, and J. Strumillo (*Acta Pol. Pharm.*, 1984, 41, 651-7; CA 104:50859y), was dissolved in chloroform (5.3 mL). Di-*tert*-butyl dicarbonate (0.63 g, 2.9 mmol) was added along with additional chloroform (3 x 0.15 mL) to aid in the transfer. The solution was stirred for 0.5 h at room temperature followed by 3 h at reflux. The solution was then diluted with ethyl acetate (20 mL) and washed with saturated aqueous sodium bicarbonate (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL) The combined organic layers were dried (sodium sulfate), decanted, and evaporated to give 549 mg (97%) of 4-(*tert*-butoxycarbonyl)-hexahydro-(2*H*)-1,4-diazepin-2-one as white crystals.

^{1}H NMR (400 MHz, CD_3OD): δ 4.08-4.02 (m, 2H), 3.58 (bt, 2H, J = 5 Hz), 3.29-3.26 (m, 2H), 1.81 (broad quintet, 2H, J = 5 Hz), 1.45 (s, 9H).

Mass spectrum (FAB) m/e = 215 (M+1).

Step B: 1-(*tert*-Butoxycarbonyl)-2,5,6,7-tetrahydro-3-methoxy-(1*H*)-1,4-diazepine.

By analogy to the procedure of Example 2, 4-(*tert*-butoxycarbonyl)-hexahydro-(2*H*)-1,4-diazepin-2-one gave 1-(*tert*-butoxycarbonyl)-2,5,6,7-tetrahydro-3-methoxy-(1*H*)-1,4-diazepine as a colorless oil in 94% yield.

^{1}H NMR (400 MHz, CD_3OD): δ 4.16-4.10 (m, 2H), 3.59 (bs, 3H), 3.56 (bt, 2H, J = 6 Hz), 3.53-3.48 (m, 2H), 1.87-1.77 (m, 2H), 1.44 (s, 9H).

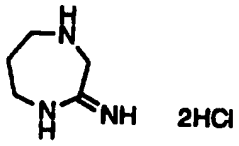
Mass spectrum (FAB) m/e = 229 (M+1).

Step C: 1-(*tert*-Butoxycarbonyl)-hexahydro-3-imino-(1*H*)-1,4-diazepine hydrochloride.

By analogy to the procedure of Example 3, 1-(*tert*-butoxycarbonyl)-2,5,6,7-tetrahydro-3-methoxy-(1*H*)-1,4-diazepine gave 1-(*tert*-butoxycarbonyl)-hexahydro-3-imino-(1*H*)-1,4-diazepine hydrochloride in quantitative yield as white crystals.

^{1}H NMR (400 MHz, CD_3OD): δ 4.36 (bs, 2H), 3.69-3.62 (m, 2H), 3.60-3.55 (m, 2H), 1.84-1.76 (m, 2H), 1.47 (s, 9H).

EXAMPLE 147



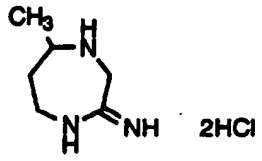
Hexahydro-2-imino-(1*H*)-1,4-diazepine dihydrochloride.

By analogy to the procedure of Example 130 (Step D), 1-(*tert*-butoxycarbonyl)-hexahydro-3-imino-(1*H*)-1,4-diazepine hydrochloride salt gave hexahydro-2-imino-(1*H*)-1,4-diazepine dihydrochloride as a fine white solid in quantitative yield.

^{1}H NMR (400 MHz, CD3OD): δ 4.38 (s, 2H), 3.72-3.68 (m, 2H), 3.52 (t, 2H, J = 5.5 Hz), 2.08 (quintet, 2H, J = 5.5 Hz).

Mass spectrum (FAB) m/e = 114 (M-2HCl+1).

EXAMPLE 148



Hexahydro-2-imino-5-methyl-(1*H*)-1,4-diazepine dihydrochloride.

Step A: *N*-(2-Cyano-1-methylethyl)glycine ethyl ester.

Aqueous sodium hydroxide (2.5 *N*, 13 mL, 32.5 mmol) was added to a mixture of 4.54 g (32.5 mmol) of glycine ethyl ester hydrochloride in 6 mL of ethanol. The solution was cooled in an ice bath and 2.4 g (35.6 mmol) of crotonitrile was added in portions over 5 min. After 20 min, the ice bath was removed and the reaction was stirred 1.5 h at 25 °C followed by 3.5 h at 70 °C. The reaction was cooled to room temperature, 5 g of sodium chloride was added, and the mixture was extracted with 2 x 35 mL of ethyl acetate. The organic extracts were dried over sodium sulfate, decanted, and evaporated. The residue was dissolved in methanol, filtered through a 0.45 micron membrane, and evaporated to give 1.30 g (24% yield) of *N*-(2-cyano-1-methylethyl)glycine ethyl ester as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20 (q, 2 H, H=7 Hz), 3.47 (d, 1H, J = 16 Hz), 3.41 (d, 1H, J = 16 Hz), 3.05 (sextet, 1H, J = 7 Hz), 2.49-2.38 (m, 2H), 1.29 (t, 3H, J = 7 Hz), 1.27 (d, 3H, J = 7 Hz).

Step B: Hexahydro-5-methyl-(2*H*)-1,4-diazepin-2-one.

N-(2-cyano-1-methylethyl)glycine ethyl ester (1.30 g, 7.64 mmol) was dissolved in 4.5 mL of methanol. Raney nickel (70 mg) was added and the reaction vessel was pressurized with 1000 psi of hydrogen and heated to 50 °C for 6 h and to 100 °C for 4 h. The supernatant was decanted and filtered through a 0.45 micron membrane and the catalyst

was washed with 3 x 3 mL of methanol. The combined filtrate was evaporated and the residue was chromatographed on 60 g of silica gel eluting with 5-7% methanol in dichloromethane to give 0.33 g of colorless oil. Chromatography on 15 g of silica gel eluting with 20% methanol in ethyl acetate gave 217 mg (22% yield) of pure hexahydro-5-methyl-(2*H*)-1,4-diazepin-2-one.

^{1}H NMR (400 MHz, CD_3OD): δ 3.52 (d, 1H, J = 15 Hz), 3.37 (d, 1H, J = 15 Hz), 3.35 (1H, partially obscured by solvent), 3.23 (ddd, 1H, J = 15, 6, 2 Hz), 2.89 (dqd, 1H, J = 10, 6, 3 Hz), 1.82 (dddd, J = 14, 6, 3, 1 Hz), 1.39 (m, 1H), 1.12 (d, 3H, J = 6 Hz).

Mass spectrum (FAB) m/e = 129 (M+1).

Step C: 4-(*tert*-Butoxycarbonyl)-hexahydro-5-methyl-(2*H*)-1,4-diazepin-2-one.

Hexahydro-5-methyl-(2*H*)-1,4-diazepin-2-one (200 mg, 1.56 mmol) was dissolved in 3.0 mL of chloroform and di-*tert*-butyl dicarbonate (0.37 g, 1.69 mmol) was added with 0.4 mL of chlorform. The solution was stirred at room temperature for 0.5 h and then at reflux for 4.5 hr. The solution was diluted with 20 mL of ethyl acetate and washed with 5 mL of saturated aqueous sodium bicarbonate and 5 mL of saturated aqueous sodium chloride. The aqueous layers were extracted in succession with 10 mL of ethyl acetate. The combined organic layers were dried (sodium sulfate), decanted, and evaporated to give 360 mg (100% yield) of 4-(*tert*-butoxycarbonyl)-hexahydro-5-methyl-(2*H*)-1,4-diazepin-2-one as almost colorless crystals.

^{1}H NMR (400 MHz, CD_3OD): δ 4.39-4.02 (m, 2H), 3.80 (bd, 1H, J = 17 Hz), 3.19 (dd, 1H, J = 14, 7 Hz), 3.13-3.02 (m, 1H), 2.13 (dt, 1H, J = 15, 6 Hz), 1.80 (dtd, 1H, J = 15, 10, 2 Hz), 1.46 (s, 9H), 1.16 (d, 3H, J = 6.5 Hz).

Mass spectrum (ESI) m/e = 229 (M+1).

Step D: 1-(*tert*-Butoxycarbonyl)-2,5,6,7-tetrahydro-3-methoxy-7-methyl-(1*H*)-1,4-diazepine.

By analogy to the procedure of Example 2, 4-(*tert*-butoxycarbonyl)-hexahydro-5-methyl-(2*H*)-1,4-diazepin-2-one gave 1-(*tert*-butoxycarbonyl)-2,5,6,7-tetrahydro-3-methoxy-7-methyl-(1*H*)-1,4-diazepine as an almost colorless oil in 86% yield.

^{1}H NMR (400 MHz, CD_3OD): δ 4.55-4.10 (m, 2H), 3.75-3.55 (m, 2H), 3.60 (s, 3H), 3.40 (dd, 1H, J = 16, 11 Hz), 2.02-1.90 (m, 1H), 1.65 (dt, 1H, J = 15, 11 Hz), 1.45 (s, 9H), 1.12 (d, 3H, J = 6.5 Hz).

Step E: 4-(*tert*-Butoxycarbonyl)-hexahydro-2-imino-5-methyl-(1*H*)-1,4-diazepine hydrochloride.

By analogy to the procedure of Example 3, 1-(*tert*-butoxycarbonyl)-2,5,6,7-tetrahydro-3-methoxy-7-methyl-(1*H*)-1,4-diazepine gave 4-(*tert*-butoxycarbonyl)-hexahydro-2-imino-5-methyl-(1*H*)-1,4-diazepine hydrochloride in quantitative yield.

^{1}H NMR (400 MHz, CD_3OD): δ 4.60-4.20 (m, 3H), 4.53 (dd, 1H, J = 14, 7 Hz), 3.34-3.23 (partially obscured by solvent, 1H), 2.19-2.07 (m, 1H), 1.93 (dt, 1H, J = 15, 10 Hz), 1.19 (d, 3H, J = 7 Hz).

Mass spectrum (ESI) m/e = 228 (M-HCl+1).

Step F: Hexahydro-2-imino-5-methyl-(1*H*)-1,4-diazepine dihydrochloride.

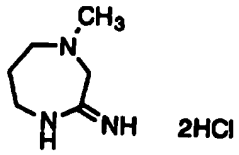
By analogy to the procedure of Example 130 (Step D), 4-(*tert*-butoxycarbonyl)-hexahydro-2-imino-5-methyl-(1*H*)-1,4-diazepine

hydrochloride gave hexahydro-2-imino-5-methyl-(1*H*)-1,4-diazepine dihydrochloride as a hygroscopic brittle foam in quantitative yield.

^{1}H NMR (400 MHz, CD_3OD): δ 4.52 (d, 1H, J = 15 Hz), 4.18 (d, 1H, J = 15 Hz), 3.76-3.62 (m, 3H), 2.17 (dm, 1H, J = 15 Hz), 1.89-1.77 (m, 1H), 1.43 (d, 3H, J = 6 Hz).

Mass spectrum (FAB) m/e = 128 (M-2HCl+1).

EXAMPLE 149



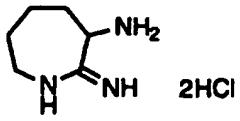
Hexahydro-2-imino-4-methyl-(1*H*)-1,4-diazepine hydrochloride.

By analogy to the procedure of Example 140 step F, 2,5,6,7-tetrahydro-3-methylthio-1-methyl-(1*H*)-1,4-diazepine (prepared by the route of R. Guryn, *Polish J. Chem.*, 1989, 63, 265-271; CA 112:178916x) gave hexahydro-2-imino-4-methyl-(1*H*)-1,4-diazepine hydrochloride. The crude product obtained from 124 mg (0.784 mmol) of the starting iminothioether was dissolved in 0.55 mL of chloroform at 45 °C and 0.25 mL of ethyl acetate was added. After cooling to room temperature, the resulting pale tan crystals were separated and dried under vacuum to give 108 mg (84% yield) of product.

^{1}H NMR (400 MHz, CD_3OD): δ 3.68 (s, 3H), 3.54-3.50 (m, 2H), 2.97 (t, 2H, J = 5.5 Hz), 1.80 (quintet, 2H, J = 5 Hz).

Mass spectrum (FAB) m/e = 128 (M-HCl+1).

EXAMPLE 150



3-Amino-hexahydro-2-imino-(1*H*)-azepine dihydrochloride.

Step A: 3-(*tert*-Butoxycarbonylamino)-epsilon-caprolactam.

3-Amino-epsilon-caprolactam (2.00 g, 15.6 mmol) was dissolved in 25 mL of chloroform and di-*tert*-butyl dicarbonate (3.70 g, 16.9 mmol) was added with 5 mL of chloroform. The solution was stirred at room temperature for 2 hr. The reaction was diluted with 10 mL of chloroform and washed with 2 x 10 mL of 2 *N* aqueous hydrochloric acid, 10 mL of saturated aqueous sodium bicarbonate, and 10 mL of saturated aqueous sodium chloride. The combined organic layers were dried (sodium sulfate), decanted, and evaporated to give an almost colorless crystalline solid. This material was dissolved in 15 mL of hexane and 20 mL of ethyl acetate at 75 °C, cooled to room temperature, and filtered to give 2.02 g (57% yield) of 3-(*tert*-butoxycarbonylamino)-epsilon-caprolactam as white crystals.

^{1}H NMR (400 MHz, CD_3OD): δ 4.26 (d, 1H, J = 10 Hz), 3.29-3.16 (m, 2H), 2.03-1.70 (m, 4H), 1.60-1.27 (m, 2H), 1.44 (s, 9H).

Mass spectrum (FAB) m/e = 229 (M+1).

Step B: 3-(*tert*-Butoxycarbonylamino)-4,5,6,7-tetrahydro-2-methoxy-(3*H*)-azepine.

By analogy to the procedure of Example 2, 3-(*tert*-butoxycarbonylamino)-epsilon-caprolactam gave 3-(*tert*-

butoxycarbonylamino)-4,5,6,7-tetrahydro-2-methoxy-(3*H*)-azepine as a colorless oil in 95% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.38 (bd, 1H, J = 6 Hz), 4,58 (bdd, 1H, J = 10, 8 Hz), 3.68-3.62 (m, 1H), 3.29 (t, 1H, J = 12 Hz), 1.99-1.70 (m, 4H), 1.46 (s, 9H), 1.46-1.22 (m, 2H).

Step C: 3-(*tert*-Butoxycarbonylamino)-hexahydro-2-imino-(1*H*)-azepine hydrochloride.

3-(*tert*-Butoxycarbonylamino)-4,5,6,7-tetrahydro-2-methoxy-(3*H*)-azepine (503 mg, 2.08 mmol) was dissolved in 6.0 mL of ethanol and 111 mg (2.08 mmol) of ammonium chloride was added. The mixture was heated to reflux for 3 h, cooled to room temperature, and evaporated. The residue was dissolved in 4 mL of chloroform, filtered through a 0.45 micron membrane, and evaporated under a stream of nitrogen to a weight of 1.18 g. Dioxane (4.0 mL) was added and the mixture was stirred briefly until it became homogeneous. After crystals had formed, the mixture was cooled to 0 °C and filtered to give 3-(*tert*-butoxycarbonylamino)-hexahydro-2-imino-(1*H*)-azepine hydrochloride as white crystals (623 mg, 85% yield) which retained 1 equivalent of dioxane.

^{1}H NMR (400 MHz, CD_3OD): δ 4.57 (d, 1H, J = 10 Hz), 3.57-3.46 (m, 2H), 2.06-1.94 (m, 2H), 1.89-1.66 (m, 3H), 1.51-1.42 (m, 1H), 1.46 (s, 9H).

Mass spectrum (FAB) m/e = 228 (M+1).

Step D: 3-Amino-hexahydro-2-imino-(1*H*)-azepine dihydrochloride.

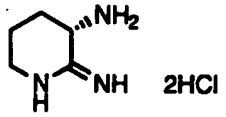
By analogy to the procedure of Example 130 (Step D), 3-(*tert*-butoxycarbonylamino)-hexahydro-2-imino-(1*H*)-azepine,

hydrochloride salt gave 3-amino-hexahydro-2-imino-(1*H*)-azepine dihydrochloride as fine white crystals in quantitative yield.

^{1}H NMR (400 MHz, CD_3OD): δ 4.71 (dd, 1H, J = 10, 1.5 Hz), 3.61-3.50 (m, 2H), 2.15-1.82 (m, 5H), 1.60-1.47 (m, 1H).

Mass spectrum (FAB) m/e = 128 (M-2HCl+1).

EXAMPLE 151



(*S*)-3-Amino-2-iminopiperidine dihydrochloride.

Step A: (*S*)-3-(*tert*-Butoxycarbonylamino)-2-piperidone.

1-Hydroxybenzotriazole (960 mg, 7.10 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.36 g, 7.09 mmol) were added to a stirred suspension of 1.50 g (6.46 mmol) of *N*-alpha-(*tert*-butoxycarbonyl)-L-ornithine in 15 mL of *N,N*-dimethylformamide. After stirring overnight at room temperature, most of the solvent was removed on a rotary evaporator and the residue was diluted with 50 mL of ethyl acetate. The mixture was washed with 15 mL each of 2 *N* aqueous hydrochloric acid, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride. The organic layer was dried (sodium sulfate), decanted, and evaporated to give 706 mg (55% yield) of (*S*)-3-(*tert*-butoxycarbonylamino)-2-piperidone as a colorless viscous syrup.

^{1}H NMR (400 MHz, CD_3OD): δ 4.02-3.92 (m, 1H), 3.30-3.22 (m, 2H), 2.15-2.05 (m, 1H), 1.97-1.70 (m, 3H), 1.45 (s, 9H).

Step B: (*S*)-3-(*tert*-Butoxycarbonylamino)-3,4,5,6-tetrahydro-2-methoxypyridine.

By analogy to the procedure of Example 2, (*S*)-3-(*tert*-butoxycarbonylamino)-2-piperidone gave (*S*)-3-(*tert*-butoxycarbonylamino)-3,4,5,6-tetrahydro-2-methoxypyridine as white crystals in (83% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.85-4.75 (bs, 1H), 4.19-4.09 (bs, 1H), 3.63 (s, 3H), 3.49 (t, 2H, J = 6 Hz), 2.12-2.02 (m, 1H), 1.86-1.61 (m, 3H), 1.46 (s, 9H).

Mass spectrum (FAB) m/e = 229 (M+1).

Step C: (*S*)-3-(*tert*-Butoxycarbonylamino)-2-iminopiperidine hydrochloride.

By analogy to the procedure of Example 3, (*S*)-3-(*tert*-butoxycarbonylamino)-3,4,5,6-tetrahydro-2-methoxypyridine gave (*S*)-3-(*tert*-butoxycarbonylamino)-2-iminopiperidine hydrochloride as white crystals in quantitative yield.

^{1}H NMR (400 MHz, CD_3OD): δ 4.40-4.33 (m, 1H), 3.45-3.30 (m, 2H), 2.10-1.84 (m, 4H), 1.47 (s, 9H).

Mass spectrum (FAB) m/e = 214 (M-HCl+1).

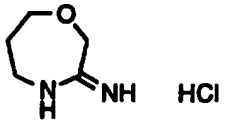
Step D: (*S*)-3-Amino-2-iminopiperidine dihydrochloride.

By analogy to the procedure of Example 130 (Step D), (*S*)-3-(*tert*-butoxycarbonylamino)-2-iminopiperidine hydrochloride gave (*S*)-3-amino-2-iminopiperidine dihydrochloride as a white crystalline solid in quantitative yield.

^{1}H NMR (400 MHz, CD_3OD): δ 4.48 (t, 1H, J = 6 Hz), 3.47 (t, 2H, J = 6 Hz), 2.37-2.24 (m, 1H), 2.08-1.90 (m, 3H).

Mass spectrum (FAB) m/e = 114 (M-2HCl+1).

EXAMPLE 152



Hexahydro-3-imino-1,4-oxazepine hydrochloride.

Step A: 2,5,6,7-Tetrahydro-3-methoxy-1,4-oxazepine.

Using the method described Example 2, 4,5,6,7-tetrahydro-(2*H*)-1,4-oxazepin-3-one (prepared by the method of S. Suzuki, U.S. patent 4126614, 1978; CA 90:138397) was converted into 2,5,6,7-tetrahydro-3-methoxy-1,4-oxazepine.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.18 (s, 2H), 3.87 (t, 2H, J = 6 Hz), 3.64-3.60 (m, 2H), 3.58 (s, 3H), 1.93-1.86 (m, 2H).

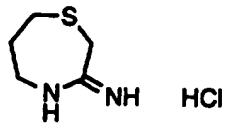
Step B: Hexahydro-3-imino-1,4-oxazepine hydrochloride.

Using the method described in Example 3, 2,5,6,7-tetrahydro-3-methoxy-1,4-oxazepine was converted into hexahydro-3-imino-1,4-oxazepine hydrochloride.

^{1}H NMR (400 MHz, CD_3OD): δ 4.47 (s, 2H), 3.96 (t, 2H, J = 5 Hz), 3.64-3.60 (m, 2H), 1.90 (quintet, 2H, J = 5 Hz).

Mass spectrum (FAB): m/e = 115 (M-HCl+1).

EXAMPLE 153



Hexahydro-3-imino-1,4-thiazepine hydrochloride.

Step A: 4,5,6,7-Tetrahydro-(2*H*)-1,4-thiazepin-3-thione.

Phosphorus pentasulfide (1.18 g, 2.66 mmol as P_4S_{10}) and sodium bicarbonate (3.56 g, 42.5 mmol) were added to a stirred solution of 500 mg (3.81 mmol) 4,5,6,7-tetrahydro-(2*H*)-1,4-thiazepin-3-one (prepared by the method of M.F. Shostakovskii, et al. *Zh. Obshch. Khim.*, 1961, 31, 1453; CA 55:22177g) in 15 mL of dry dioxane and the mixture was stirred at 75 °C for 4 h. The solvent was removed *in vacuo*, water (15 mL) was cautiously added, and the mixture was heated to 50 °C for 1 h. The reaction was cooled to room temperature and sodium chloride (6.1 g) was added followed by 40 mL of dichloromethane. To facilitate separation of the layers, 30 mL of saturated aqueous sodium chloride and 100 mL of ethyl acetate were also added. The aqueous layer was extracted with 3 x 40 mL of ethyl acetate. The combined organic layers were dried (sodium sulfate), decanted, and evaporated. The crude product was chromatographed on 30 g silica gel, eluting with 1.25 L of 20% ethyl acetate/hexane and 200 mL of 5% of ethyl acetate/dichloromethane to give 380 mg (68% yield) of 4,5,6,7-tetrahydro-(2*H*)-1,4-thiazepin-3-thione as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (bs, 1H), 3.74 (s, 2H), 3.51-2.44 (m, 2H), 2.92-2.87 (m, 2H), 1.97 (quintet, 2H, J = 5 Hz).

Mass spectrum (FAB): m/e = 148 (M+1).

Step B: 2,5,6,7-Tetrahydro-3-ethoxy-1,4-thiazepine.

Employing the method of E. Mohacsi and E.M. Gordon (*Synth. Commun.*, 1984, 14, 1159), ethyl chloroformate (0.112 mL, 1.17 mmol) was added to a mixture of 4,5,6,7-tetrahydro-(2*H*)-1,4-thiazepin-3-thione (150 mg, 1.02 mmol) and 0.30 mL of dry dioxane. The mixture was stirred and occasionally swirled for 1.5 h at room temperature. The mixture was diluted with 15 mL of ethyl acetate and washed with 15 mL of saturated aqueous sodium carbonate, 10 mL of saturated aqueous sodium carbonate, and 10 mL of saturated aqueous sodium chloride. The aqueous layers were extracted in succession with 15 mL ethyl acetate. The combined organic layers were dried (sodium sulfate), decanted, and carefully evaporated to give 158 mg of crude 2,5,6,7-tetrahydro-3-ethoxy-1,4-thiazepine as a slightly volatile yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.02 (q, 2H, J = 7 Hz), 3.54-3.50 (m, 2H), 3.28 (s, 2H), 2.88 (t, 2H, J = 5 Hz), 1.94-1.87 (m, 2H), 1.26 (t, 3H J = 7 Hz).

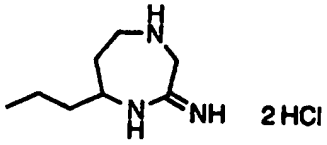
Step C: Hexahydro-3-imino-1,4-thiazepine hydrochloride.

Using the method described in Example 3, 2,5,6,7-hexahydro-3-ethoxy-1,4-thiazepine (150 mg, 0.94 mmol) was converted into the amidine hydrochloride. In this case, the crude product (138 mg) was recrystallized from methanol/ethyl acetate at 60 °C with cooling to 0 °C to give 56 mg (29% yield) of hexahydro-3-imino-1,4-thiazepine hydrochloride containing 25% ammonium chloride.

^{1}H NMR (400 MHz, CD_3OD): δ 3.62 (s, 2H), 3.60-3.58 (m, 2H), 3.01-2.97 (m, 2H), 1.95 (quintet, 2H, J = 5 Hz).

Mass spectrum (FAB): m/e = 131 (M-HCl+1).

EXAMPLE 154



Hexahydro-3-imino-5-propyl-(1*H*)-1,4-diazepine dihydrochloride.

Step A: *N*-(*t*-Butoxycarbonyl)-*N*-(3-oxohexyl)glycine ethyl ester.

1-Hexen-3-one (5.04 g, 51.3 mmol) was added to a solution of glycine ethyl ester (5.3 g, 51.3 mmol) in 50 mL of chloroform. After 3 h at room temperature, chloroform (15 mL) was added followed by portionwise addition of di-*tert*-butyl dicarbonate (12.2 g, 56 mmol). The solution was stirred overnight at room temperature and then washed with 50 mL of saturated aqueous sodium bicarbonate and 50 mL of saturated aqueous sodium chloride. The combined aqueous layers were extracted with 2 x 50 mL of ethyl acetate. The combined organic layers were dried (sodium sulfate), decanted, and evaporated. Flash column chromatography on 450 g of silica gel eluting with 10% ethyl acetate/hexane gave 13.7 g (89% yield) of *N*-(*tert*-butoxycarbonyl)-*N*-(3-oxohexyl)glycine ethyl ester as a yellow oil.

^{1}H NMR (400 MHz, CDCl3) showed two distinct rotamers in a 3:2 ratio. Rotamer A (major): δ 4.13 (q, 2H, J = 7 Hz), 3.92 (s, 2H), 3.49 (t, 2H, J = 6 Hz), 2.75 (t, 2H, J = 6 Hz), 2.37 (t, 2H, J = 7 Hz), 1.62-1.50 (m, 2H), 1.38 (s, 9H), 1.25 (t, 3H, J = 7 Hz), 0.87 (t, 3H, J = 6 Hz). Rotamer B (minor): δ 4.19 (q, 2H, J = 7 Hz), 3.97 (s, 2H), 3.46 (t, 2H, J = 6 Hz), 2.70 (t, 2H, J = 6 Hz), 2.37 (t, 2H, J = 7 Hz), 1.62-1.50 (m, 2H), 1.45 (s, 9H), 1.23 (t, 3H, J = 7 Hz), 0.89 (t, 3H, J = 6 Hz).

Mass spectrum (FAB): m/e = 202 (M-99).

Step B: *N*-(*tert*-Butoxycarbonyl)-*N*-(3-(benzylamino)hexyl)glycine ethyl ester.

Benzylamine (5.7 g, 53.2 mmol) was added to stirred solution of *N*-(*tert*-butoxycarbonyl)-*N*-(3-oxohexyl)glycine ethyl ester (8.07 g, 26.6 mmol) in 30 mL of pyridine and 30 mL of glacial acetic acid at 0 °C. A THF solution of sodium cyanoborohydride (1.0 *M*, 17.3 mL, 17.3 mmol) was added *via* syringe at 2.0 mL/h. After completion of the addition, the reaction was continued at 0 °C to room temperature overnight. The reaction was poured into a mixture prepared from 20 mL of concentrated hydrochloric acid and 230 g of ice, and extracted with 4 x 200 mL of ethyl acetate. The ethyl acetate layers were washed in succession with 500 mL of saturated aqueous sodium carbonate and 500 mL of saturated aqueous sodium chloride, dried (sodium sulfate), decanted, and concentrated to give a yellow oil. Flash column chromatography on silica gel eluting with 5-50% ethyl acetate/dichloromethane furnished 5.44 g (59% yield) of *N*-(*tert*-butoxycarbonyl)-*N*-(3-(benzylamino)hexyl)glycine ethyl ester as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) was complicated by the presence of a 5:4 mixture of rotamers: δ 7.36-7.18 (m, 4H), 4.16 (q, 2H, J = 7 Hz), 3.94-3.67 (m, 5H), 3.45-3.21 (m, 2H), 2.72-2.50 (m, 1H), 1.75-1.21 (m, 9H), 1.43 and 1.39 (two s, 9H), 0.89 (t, 3H, J = 7Hz).

Mass spectrum (ESI): m/e = 393 (M+1).

Step C: *N*-(*tert*-Butoxycarbonyl)-*N*-(3-aminohexyl)glycine ethyl ester.

A solution of 5.2 g (13.3 mmol) of *N*-(*tert*-butoxycarbonyl)-*N*-(3-(benzylamino)hexyl)glycine ethyl ester in 15 mL of ethanol and 7.5 mL of glacial acetic acid was shaken with 2.08 g of 20% palladium

hydroxide on carbon under 45-47 psi of hydrogen for 24 h. The mixture was filtered and catalyst was washed with ethanol. The filtrate was concentrated and the residue was partitioned between 100 mL of ethyl acetate and 50 mL of saturated aqueous sodium bicarbonate. The aqueous phase was extracted with 3 x 50 mL of ethyl acetate, and the combined organic layers were dried (sodium sulfate), decanted, and concentrated to give *N*-(*tert*-butoxycarbonyl)-*N*-(3-aminohexyl)glycine ethyl ester as a colorless oil in quantitative yield.

^{1}H NMR (400 MHz, CD_3OD) was complicated by the presence of a 2:1 mixture of rotamers: δ 4.21-4.14 (m, 2H), 3.97-3.86 (m, 2H), 3.59-3.50 (m, 1H), 3.43-3.17 (m, 1H), 2.80-2.68 (m, 1H), 1.75-1.65 (m, 1H), 1.50-1.23 (m, 8 H), 1.47 and 1.40 (two s, 9H), 0.96-0.90 (m, 3H). MS(FAB): m/e = 303 (M+1).

Step D: 4-(*tert*-Butoxycarbonyl)-hexahydro-7-propyl-(2*H*)-1,4-diazepin-2-one.

A solution of *N*-(*tert*-butoxycarbonyl)-*N*-(3-aminohexyl)glycine ethyl ester(3.3 g, 10.4 mmol) in 40 mL of ethanol was refluxed for 2 d. The solvent was evaporated and the residue was purified by flash chromatography on 200 g of silica gel, eluting with 20-50% ethyl acetate/dichloromethane followed by 10% methanol/dichloromethane. 4-(*tert*-Butoxycarbonyl)-hexahydro-7-propyl-(2*H*)-1,4-diazepin-2-one was isolated as 804 mg (30% yield) of white solid and 1.64 g (62%) of starting material was recovered.

^{1}H NMR (400 MHz, CD_3OD) was complicated by the presence of a mixture of rotamers: δ 4.18-4.01 (m, 2H), 3.84-3.64 (m, 1H), 3.51-3.30 (m, 2H), 1.98-1.85 (m, 1H), 1.71-1.33 (m, 5H), 1.45 (s, 9H), 0.94 (t, 3H, J=7Hz).

Mass spectrum (FAB): m/e = 157 (M-99).

Step E: 1-(*tert*-Butoxycarbonyl)-2,5,6,7-tetrahydro-3-methoxy-5-propyl-(1*H*)-1,4-diazepine.

Using the method described in Example 2, 4-(*tert*-butoxycarbonyl)-hexahydro-7-propyl-(2*H*)-1,4-diazepin-2-one was converted into 1-(*tert*-butoxycarbonyl)-2,5,6,7-tetrahydro-3-methoxy-5-propyl-(1*H*)-1,4-diazepine.

^{1}H NMR (400 MHz, CD_3OD) was complicated by the presence of two rotamers: δ 4.30 and 4.17 (two d, 1H, J = 16 Hz), 4.07-3.95 (m, 1H), 3.59 (s, 3H), 3.54-3.36 (m, 3H), 1.95-1.78 (m, 1H), 1.61-1.32 (m, 5H), 1.45 (s, 9H), 0.92 (t, 3H, J = 7 Hz).

Mass spectrum (FAB): m/e = 256 (M+1).

Step F: 1-(*tert*-Butoxycarbonyl)-3-(*tert*-butoxycarbonylimino)-hexahydro-5-propyl-(1*H*)-1,4-diazepine.

Using the method described in Example 3, 100 mg (0.373 mmol) of 1-(*tert*-butoxycarbonyl)-2,5,6,7-tetrahydro-3-methoxy-5-propyl-(1*H*)-1,4-diazepine yielded 104 mg of crude 1-(*tert*-butoxycarbonyl)-hexahydro-3-imino-5-propyl-(1*H*)-1,4-diazepine hydrochloride salt as an amber foam. Without purification, this intermediate was dissolved in 1.0 mL of chloroform and treated with 0.045 mL (41 mg, 0.36 mmol) of 1,1,3,3-tetramethylguanidine and 85 mg (0.392 mmol) of di-*tert*-butyl dicarbonate. After stirring 24 h at room temperature, the mixture was partitioned between 25 mL of chloroform and 10 mL of saturated aqueous sodium chloride. The aqueous layer was extracted with an additional 25 mL of chloroform and the organic layers were dried (sodium sulfate), decanted, and evaporated. The residue was purified by flash column chromatography on 10 g of silica gel eluting with 20% ethyl acetate/hexane to furnish 46 mg (41% yield) of 1-(*tert*-butoxycarbonyl)-3-(*tert*-butoxycarbonylimino)-hexahydro-5-propyl-(1*H*)-1,4-diazepine as a colorless film.

^{1}H NMR (400 MHz, CD_3OD): δ 4.22 (bd, 1H, J = 16 Hz), 4.02-3.84 (m, 1 H), 3.96 (d, 1H, J = 16 Hz), 3.55-3.44 (m, 1H), 3.22-3.08 (m, 1H), 1.86-1.72 (m, 1H), 1.70-1.67 (m, 1H), 1.67-1.36 (m, 4H), 1.50 (s, 9H), 1.44 (s, 9H), 0.96 (t, 3H, J = 7 Hz).

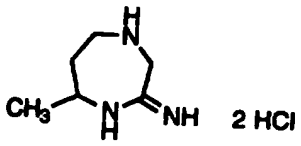
Step G: Hexahydro-3-imino-5-propyl-(1*H*)-1,4-diazepine, dihydrochloride.

Using the method described in Example 130 (Step D), 1-(*tert*-butoxycarbonyl)-3-(*tert*-butoxycarbonylimino)-hexahydro-5-propyl-(1*H*)-1,4-diazepine was converted into hexahydro-3-imino-5-propyl-(1*H*)-1,4-diazepine dihydrochloride.

^{1}H NMR (400 MHz, CD_3OD): δ 4.44 (d, 1H, J = 15 Hz), 4.06 (d, 1H, J = 15 Hz), 3.88 (q, 1H, J = 7 Hz), 3.61 (dt, 1H, J = 14, 4 Hz), 3.40 (ddd, 1H, J = 14, 11, 3 Hz), 2.15 (dt, 1H, J = 16, 4 Hz), 1.96-1.80 (m, 2H),. 1.71-1.60 (m, 1H), 1.56-1.40 (m, 2H), 1.00 (t, 3H, J = 7 Hz).

Mass spectrum (FAB): m/e = 156 (M-2HCl+1).

EXAMPLE 155



Hexahydro-3-imino-5-methyl-(1*H*)-1,4-diazepine dihydrochloride.

Step A: *N*-(*tert*-Butoxycarbonyl)-*N*-(3-oxobutyl)glycine ethyl ester.

Using the method described in Example 154 (Step A), methyl vinyl ketone and glycine ethyl ester were combined and reacted

with di-*tert*-butyl dicarbonate to give *N*-(*tert*-butoxycarbonyl)-*N*-(3-oxobutyl)glycine ethyl ester.

^{1}H NMR (400 MHz, $CDCl_3$) showed two distinct rotamers in a 3:2 ratio. Rotamer A (major): δ 4.14 (q, 2H, J = 7 Hz), 3.92 (s, 2H), 3.49 (t, 2H, J = 6 Hz), 2.79 (t, 2H, J = 6 Hz), 2.12 (s, 3H), 1.38 (s, 9H), 1.25 (t, 3H, J = 7 Hz). Rotamer B (minor): δ 4.14 (q, 2H, J = 7 Hz), 3.97 (s, 2H), 3.46 (t, 2H, J = 6 Hz), 2.74 (t, 2H, J = 6 Hz), 2.13 (s, 3H), 1.45 (s, 9H), 1.23 (t, 3H, J = 7 Hz).

Mass spectrum (ESI): m/e = 296 (M+Na).

Step B: *N*-(*tert*-Butoxycarbonyl)-*N*-(3-(benzylamino)butyl)glycine ethyl ester.

Using the method described in Example 154 (Step B), *N*-(*tert*-butoxycarbonyl)-*N*-(3-oxobutyl)glycine ethyl ester was converted into *N*-(*tert*-butoxycarbonyl)-*N*-(3-(benzylamino)butyl)glycine ethyl ester.

^{1}H NMR (400 MHz, $CDCl_3$) was complicated by the presence of two rotamers: δ 7.36-7.20 (m, 5H), 4.16 (bq, 2H, J = 7 Hz), 3.96-3.68 (m, 4H), 3.50-3.21 (m, 2H), 2.89-2.66 (m, 1H), 1.74-1.54 (m, 2H), 1.43 and 1.40 (two s, 9H), 1.26 and 1.24 (two q, 3H, J = 7 Hz), 1.13 and 1.10 (two d, 3H, J = 6 Hz).

Mass spectrum (ESI): m/e = 365 (M+1).

Step C: *N*-(*tert*-Butoxycarbonyl)-*N*-(3-aminobutyl)glycine ethyl ester.

Using the method described in Example 154 (Step C), *N*-(*tert*-butoxycarbonyl)-*N*-(3-(benzylamino)butyl)glycine ethyl ester was

converted into *N*-(*tert*-butoxycarbonyl)-*N*-(3-aminobutyl)glycine ethyl ester.

^{1}H NMR (400 MHz, $CDCl_3$) was complicated by the presence of two rotamers: δ 4.18 (q, 2H, J = 6 Hz), 3.99-3.86 (m, 2H), 3.58-3.49 (m, 1H), 3.42-3.17 (m, 1H), 3.07-2.89 (m, 1H), 1.72-1.44 (m, 2 H), 1.47 and 1.41 (two s, 9H), 1.30-1.24 (m, 3H), 1.15-1.10 (m, 3H).

Mass spectrum (ESI): m/e = 275 (M+1).

Step D: 4-(*tert*-Butoxycarbonyl)-hexahydro-7-methyl-(2*H*)-1,4-diazepin-2-one.

Using the method described in Example 154 (Step D), *N*-(*tert*-butoxycarbonyl)-*N*-(3-aminobutyl)glycine ethyl ester was converted into 4-(*tert*-butoxycarbonyl)-hexahydro-7-methyl-(2*H*)-1,4-diazepin-2-one.

^{1}H NMR (400 MHz, $CDCl_3$) was complicated by the presence of rotamers: δ 4.35-3.35 (m, 5H), 1.90-1.60 (m, 2H), 1.44 (s, 9H), 1.22 (d, J = 6 Hz).

Mass spectrum (ESI): m/e = 229 (M+1).

Step E: 1-(*tert*-Butoxycarbonyl)-2,5,6,7-tetrahydro-3-methoxy-5-methyl-(1*H*)-1,4-diazepine.

Using the method described in Example 2, 4-(*tert*-butoxycarbonyl)-hexahydro-7-methyl-(2*H*)-1,4-diazepin-3-one was converted into 1-(*tert*-butoxycarbonyl)-2,5,6,7-tetrahydro-3-methoxy-5-methyl-(1*H*)-1,4-diazepine.

^{1}H NMR (400 MHz, $CDCl_3$) was complicated by the presence of two rotamers: δ 4.35 and 4.14 (two d, 1H, J = 16 Hz), 3.95 (d, 1H, J = 16

Hz), 3.64-3.30 (m, 3H), 3.58 (s, 3H), 1.92-1.82 (m, 1H), 1.63-1.52 (m, 1H), 1.43 (s, 9H), 1.22 (d, 3H, J = 6 Hz).

Mass spectrum (ESI): m/e = 243 (M+1).

Step F: 1-(*tert*-Butoxycarbonyl)-hexahydro-3-imino-5-methyl-(1*H*)-1,4-diazepine hydrochloride.

Using the method described in Example 3, 1-(*tert*-butoxycarbonyl)-2,5,6,7-tetrahydro-3-methoxy-5-methyl-(1*H*)-1,4-diazepine was treated with ammonium chloride in ethanol. Recrystallization of the crude product from chloroform/dioxane yielded 1-(*tert*-butoxycarbonyl)-hexahydro-3-imino-5-methyl-(1*H*)-1,4-diazepine hydrochloride as white crystals.

^{1}H NMR (400 MHz, CD_3OD) was complicated by the presence of two rotamers: δ 4.53 and 4.45 (two d, 1H, J = 16 Hz), 4.32 and 4.21 (two d, 1H, J = 16 Hz), 4.13 (dt, 1H, J = 14, 3 Hz), 3.96-3.86 (m, 1H), 3.34-3.20 (m, 1H), 1.89-1.81 (m, 1H), 1.78-1.62 (m, 1H), 1.47 (s, 9H), 1.35 (d, 3H, J = 6 Hz).

Mass spectrum (ESI): m/e = 228 (M-HCl+1).

Step G: Hexahydro-3-imino-5-methyl-(1*H*)-1,4-diazepine dihydrochloride.

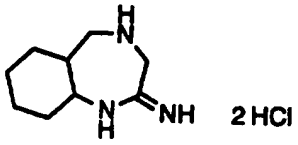
Using the method described in Example 130 (Step D), 1-(*tert*-butoxycarbonyl)-hexahydro-3-imino-5-methyl-(1*H*)-1,4-diazepine hydrochloride was converted into hexahydro-3-imino-5-methyl-(1*H*)-1,4-diazepine dihydrochloride.

^{1}H NMR (400 MHz, CD_3OD): δ 4.54 (d, 1H, J = 15 Hz), 4.21 (d, 1H, 15 Hz), 4.10-4.01 (m, 1H), 3.64 (dt, 1H, J = 14, 3 Hz), 3.40 (td, 1H, J =

14, 3 Hz), 2.08 (dtd, 1H, J = 14, 3, 1 Hz), 2.01-1.88(m, 1H), 1.43 (d, 3H, J = 7 Hz).

Mass spectrum (FAB): m/e = 128 (M-2HCl+1).

EXAMPLE 156



2-Imino-decahydro-cis-1,4-benzo(e)diazepine dihydrochloride

Step A: N-2-Nitrophenylmethyl-glycine methyl ester

To a solution of glycine methyl ester hydrochloride (8.31 g, 66.2 mmol) in 150 ml MeOH were added 2-nitrobenzaldehyde (10 g, 66.2 mmol) and 27 g of powdered molecular sieves (3A) . After stirring at room temperature overnight, sodium cyanoborohydride (12.5 g,199 mol) in 150 ml of THF was added, then the reaction mixture was further stirred for 8 h. The solvent was removed under reduced pressure. The residue was suspended in EtOAc and filtered throught a pad of celite. The filtrate was washed with sat. $NaHCO_3$. The aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered , concentrated and chromatographed on silica gel eluting with hexane-EtOAc to give 2.94 g of the desired product.

^{1}H-NMR (500MHz, $CDCl_3$): δ 7.97(1H, d, J=8Hz), 7.65(1H, d, J=8Hz), 7.6(1H, t, J=8Hz), 7.44(1H, t, J=8Hz), 4.11(2H, s), 3.73(3H, s), 3.47(2H, s).

Mass Spectrum m/e = 225 (M^++1)

Step B: N-(2-Aminophenyl)methyl-N-t-butyloxycarbonyl-glycine methyl ester

To a solution of N-2-nitrophenylmethyl-glycine methyl ester (2.94 g, 13.1 mmol) in 80 ml CH_3CN was added di-t-butyl dicarbonate (3.43 g, 15.7 mmol) and diisopropylethylamine (6.8 ml, 39 mmol). After stirring at room temperature overnight, the solvent was removed under reduced pressure, diluted with EtOAc, washed with NH_4Cl solution. The aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and chromatographed on silica gel eluting with hexane-EtOAc to give 4.11 g of N-2-nitrophenylmethyl-N-t-butyloxycarbonyl-glycine methyl ester. This material was dissolved in 150 ml of MeOH and hydrogenated in a Parr shaker (50 psi) with 164 mg of 10% Pd/C overnight. The reaction mixture was then filtered through a pad of celite and was concentrated. The residue was chromatographed on silica gel eluting with hexane-EtOAc to give 3.6 g of the desired product.

^{1}H-NMR (500MHz, $CDCl_3$): δ 7.1(1H, t, J=7.6Hz), 6.97(1H, d, J=7Hz), 6.66(2H, multiplet), 4.47(2H, s), 4.41(2H, br. s), 3.71(3H, s), 1.46(9H, s).

Mass spectrum m/e = 295 (M^++1).

Step C: 4-t-Butyloxycarbonyl-4,5-dihydro-1H-benzo-(e)-1,4-diazepin-2(3H)-one

To a 150 ml DMF solution of N-(2-aminophenyl)methyl-N-t-butyloxycarbonyl-glycine methyl ester (3.6 g, 12.2 mmol) was added NaH (308 mg, 12.8 mmol). After stirring overnight, DMF was removed under reduced pressure. The residue was diluted with CH_2Cl_2 and was washed with aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 twice. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to give pale yellow fluffy solid. This

material was suspended in hexanes : EtOAc = 5:1. The solid material was collected by suction filtration to give 2.53 g of desired product as white solid.

^{1}H-NMR (500MHz, $CDCl_3$): δ 8.1-6.95(4H, br m), 4.6-4.2(4H, br m), 1.4(9H, br m).

Mass spectrum m/e = 263 (M^++1), 163(M^+-Boc).

Step D: 4-t-Butyloxycarbonyl-octahydro-1H-benzo-(e)-1,4-diazepin-2(3H)-one

To HOAc (50 ml) solution of the 4-t-butyloxycarbonyl-4,5-dihydro-1H-benzo-(e)-1,4-diazepin-2(3H)-one (1.0 g ,3.8 mmol) was added 500 mg of PtO_2. This mixture was hydrogenated in a Parr shaker (50 psi) overnight, then filtered through a pad of celite, and concentrated. The residue was diluted with EtOAc, washed with sat $NaHCO_3$ twice, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was chromatographed on silica gel eluting with hexane-EtOAc to give 965 mg of the desired product.

Mass spectrum m/e = 269(M^++1), 169(M^+-Boc).

Step E: 4-t-Butyloxycarbonyl-2-imino-decahydro-cis-1,4-benzo(e)diazepine hydrochloride

This compound was prepared following the procedure described in examples 2 and 3.

Mass spectrum m/e = 268(M^++1)

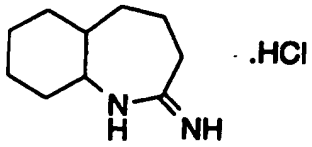
Step F: 2-Imino-decahydro-cis-1,4-benzo(e)diazepine dihydrochloride

To EtOAc (1 mL) solution of 30 mg (0.1 mmol) of 4-t-butyloxycarbonyl-2-imino-decahydro-cis-1,4-benzo(e)diazepine hydrochloride was added 2ml of EtOAc solution of anhydrous HCl. After stirring for 1h, the solvent was removed under reduced pressure to give 21.6 mg of the desired compound.

Mass spectrum m/e = 168 (M^++1)

EXAMPLE 157

2-Imino-decahydro-cis-3H-benz(e)azepin hydrochloride



Step A: 4,5-Dihydro-3H-benz(e)azepin-2(1H)-one

Sodium azide (1.11 g, 17 mmol) was suspended in 7 mL $CHCl_3$ / 1.3 mL H_2O and cooled to 0 °C in an ice bath. Sulfuric acid (0.5 mL) was added dropwise, and the suspension was warmed to room temperature. After 15 minutes, the $CHCl_3$ layer was removed and dried with Na_2SO_4. After filtering, the $CHCl_3$ solution was added to a solution of 1.0g a-tetralone (6.84 mmol) in 2mL $CHCl_3$. The combined solutions were cooled to 0° C in an ice bath, and 2.2 mL sulfuric acid was added dropwise. After addition, the solution was warmed to 45° C for 45 minutes, then cooled to room temperature. The H_2SO_4 phase was diluted with H_2O and cooled to 0° C. A 50% aqueous solution of NaOH was added dropwise until pH=13. The resulting suspension was diluted with H_2O / EtOAc and stirred until the solids were dissolved. The aqueous phase was extracted with ethyl acetate, and the combined organic layers were dried with Na_2SO_4, filtered, concentrated, and chromatographed with hexanes / ethyl acetate to isolate 0.64g (58%) of the product.

^{1}H NMR 500 MHz ($CDCl_3$): 2.18-2.27 (m, 4H), 2.76 (t, 2H), 7 (app. d, 1H), 7.12 (app. t, 1H), 7.23 (app.t, 2H).

Mass spectrum m/e = 162 (M+1)

Step B: Octahydro-cis-3H-benz(e)-azepin-2(1H)-one

4,5-Dihydro-3H-benz(e)azepin-2(1H)-one (0.5 g, 3.1 mmol) was dissolved in 4 mL acetic acid and 0.25 g platinum (IV) oxide was added. The mixture was shaken under a hydrogen atmosphere at 50 psi overnight. The mixture was filtered through Celite, which was then washed with 10mL ethyl acetate. The collected solution was concentrated to a crystalline solid. Chromatography with hexanes / ethyl acetate isolated 0.45g (87%) of product.

1H NMR (400MHz, $CDCl_3$) 1.1-1.9 (m, 12H), 2.45 (m, 3H), 3.76 (app. s 1H), 5.2 (br s 1H).

Mass spectrum m/e = 168 (M+1)

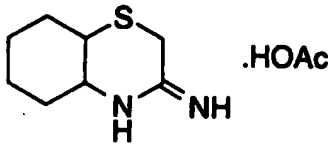
Step C: 2-Imino-decahydro-3H-benz(e)azepin hydrochloride

The title compound was prepared following the procedure described in Examples 2 and 3.

^{1}H NMR (500 MHz, CD_3OD) 1.0-2.4 (m, 13H), 2.58-2.76 (m, 3H), 3.34 (m, 1H), 3.98 (s, 1H).

Mass spectrum m/e = 167 (M+1)

EXAMPLE 158

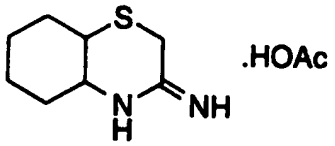


Trans-Octahydro-3-imino-2H-1,4-benzthiazine, acetic acid salt

The title compound was prepared from trans-2-aminocyclohexanol hydrochloride according to the procedure described in Example 140.

Mass spectrum m/e = 171 (M+1)

EXAMPLE 159



Cis-Octahydro-3-imino-2H-1,4-benzthiazine, acetic acid salt

Step A: 2-Ethoxycarbonylmethylthio-cyclohexanone

A solution of 1.14 mL (10 mmol) of 2-chlorocyclohexanone in 15 mL of EtOH was treated with 1.1 mL (10 mmol) of ethyl 2-mercaptoacetate and 1.38 g (10 mmol) of K_2CO_3. After stirring for 1 h the reaction mixture was partitioned between water and Et_2O:EtOAC. The organic layer was washed with water, brine, dried and concentrated. Purification of the residue by chromatography using a gradient of 10-20% EtOAc-hexane furnished 2.0 g of the title compound.

Step B: Cis-Hexahydro-1,4-benzthiaxazin-3(4H)-one

To a solution of 0.43 g (2 mmol) of 2-ethoxycarbonylmethylthio-cyclohexanone in 5 mL of MeOH, 0.12 g (2.24 mmol) of NH_4Cl was added and strieed for 10 min to allow some of NH_4Cl to dissolve. A THF solution of $NaCNBH_3$ (1M, 2.3 mL) was dropwise added to this mixture with a syringe pump over 40 min. White precipitate was formed as the reducing agent was added. After stirring for 4 h, the reaction was quenched by adding $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with water, brine, dried and concentrated. The residue was dissolved in 3 mL of EtOH, heated to 50 °C for 2 h then allowed to stand for 2 d. The solution was concentrated and the residue was chromatographed using a gradient of 20-100% EtOAc-hexane to isolate 30 mg of the desired product along with 53 mg of the trans-hexahydro-1,4-benzthiaxazin-3(4H)-one.

^1H NMR (CDCl3): 1.2-2.0 (m, 8H), 3.08 (m, 1H), 3.22 and 3.34 (AB q, 2H, J=16 Hz), 3.75 (m, 1H), 6.3 (br s, 1H).

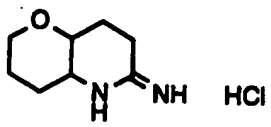
Step C: Cis-Octahydro-3-imino-2H-1,4-benzthiazine, acetic acid salt

The title compound was prepared from cis-hexahydro-1,4-benzthiaxazin-3(4H)-one by the method of Example 140 step D and E.

^1H NMR (CD3OD): 1.35-2.1 (m, 8H), 1.95 (s, 3H), 3.4 (m, 1H), 3.46 (d, 1H), 3.74 (m, 1H), 3.79 (d, 1H).

Mass spectrum m/e = 171 (M+1)

EXAMPLE 160



2-Imino-5(6H)-oxa-*cis*-hexahydro-(1H)-quinoline hydrochloride

Step A: 1-Benzyl-3,4,6,7-tetrahydro-pyrindin-2,5-dione

To a solution of 3-benzylamino-cyclopent-2-en-1-one (5.0 g, 0.027 mol) in dry tetrahydrofuran (THF) (120 mL) at reflux temperature was added over 90 min. a solution of acryloyl chloride (3.15 g, 0.035 mol) in THF (60 mL). Stirring at reflux temperature was maintained for an additional 10 hours. The reaction mixture was cooled and washed with saturated sodium bicarbonate solution (100 mL). The aqueous layer was extracted with diethyl ether (2 x 100 mL), and the combined organic layers dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (20-30% acetone/hexane) to afford the title compound as an oil that solidified upon standing; yield 2.17 g (34%).

^1H NMR (400 MHz, $CDCl_3$): d 2.45 (m, 2H); 2.52 (m, 2H); 2.63 (m, 2H); 2.73 (t, 2H); 4.91 (s, 2H); 7.18-7.36 (m, 5H).

Mass spectrum: m/e 242 (M + 1).

Step B: 1-Benzyl-*cis*-hexahydro-pyrindin-2,5-dione

A mixture of 1-benzyl-3,4,6,7-tetrahydro-pyrindin-2,5-dione (780 mg, 3.23 mmol) and sodium carbonate (156 mg) in ethanol (40 mL) was hydrogenated in the presence of 10% palladium-on-charcoal (390 mg) at 50 psi for 48 h. The catalyst was removed by filtration through Celite, washed with methanol, and the combined filtrate and washings evaporated. TLC indicated a mixture of the saturated ketone and slower-moving alcohol. The crude product was therefore subjected to oxidation with tetrapropylammonium perruthenate(VII) (TPAP) (52 mg, 0.147 mmol) in methylene chloride (8 mL) in the presence of 4-methylmorpholine N-oxide (514 mg, 4.39 mmol), and powdered 4A molecular sieves ((1.47 g). After stirring for 1 h at room temperature, the reaction mixture was placed on top of a column of silica gel (30 g) (packed as a slurry in 20% acetone/hexane). Elution with the same solvent system afforded the title compound; yield 540 mg (69%).

^{1}H NMR (400 MHz, $CDCl_3$): d 1.89 (m, 1H); 1.96-2.09 (m, 2H); 2.16-2.37 (m, 3H); 2.42 (m, 2H); 2.50 (m, 1H); 3.98 (m, 1H); 4.25 (d, 1H); 5.18 (d, 1H); 7.21-7.32 (m, 5H).

Mass spectrum: m/e 244. (M + 1).

Step C: 1-Benzyl-5-oxa-*cis*-hexahydro-quinoline-2,6-dione and 1-benzyl-6-oxa-*cis*-hexahydro-quinoline-2,5-dione

To a solution of 1-benzyl-*cis*-hexahydro-pyrindin-2,5-dione (195 mg, 0.801 mmol) in chloroform (5 mL) was added p-toluenesulfonic acid (10 mg) and a solution of m-chloroperbenzoic acid (138 mg, 0.801 mmol) in chloroform (5 mL). The reaction mixture was stirred for 2 days at room temperature and then evaporated. The residue was chromatographed on silica gel (30% acetone/hexane) to afford a mixture (~55:45) of the title compounds; yield 73 mg (35%).

^{1}H NMR (400 MHz, $CDCl_3$) for 1-benzyl-5-oxa-*cis*-hexahydro-quinoline-2,6-dione only: d 2.72 (septet, 1H); 3.63 (q, 1H); 4.01 (d, 1H); 4.67 (m, 1H); 5.37 (d, 1H).

Step D: 1-Benzyl-5(6H)-oxa-*cis*-hexahydro-quinoline-2-one

To a solution of the mixture of lactones from Step C (65 mg, 0.251 mmol) in THF (1 mL) cooled to -78°C was added diisobutylaluminum hydride (1.0M solution in hexanes) (0.50 mL, 0.502 mmol). After stirring for 1 hour at -78 °C, the reaction was quenched by pouring into saturated ammonium chloride solution at 0 °C. The mixture was extracted with chloroform (2 x 25 mL) and the combined organic extracts dried (Na2SO4). The crude lactol was treated with triethylsilane (41 mL, 0.258 mmol) and boron trifluoride-etherate (23 mL, 0.189 mmol) in methylene chloride (1 mL) at -20 °C for 1 hour. Additional triethylsilane (27 mL) and boron trifluoride-etherate (21 mL) were added,

and the mixture was stirred overnight at room temperature. The mixture was diluted with methylene chloride, washed with saturated sodium bicarbonate solution, dried (Na_2SO_4) and evaporated. Chromatography on silica gel (20% acetone/hexane) afforded the title compound as the faster-moving on TLC of the two products; yield 5.2 mg.

^1H NMR (400 MHz, $CDCl_3$): d 1.77 (m, 1H); 2.09 (m, 2H); 2.45 (dq, 1H); 2.77 (septet, 1H); 3.29 (m, 1H); 3.51 (m, 1H); 3.75 (m, 1H); 3.88 (m, 1H); 4.11 (d, 1H); 5.31 (d, 1H); 7.21-7.32 (m, 5H).

Mass spectrum: m/e 246 (M + 1).

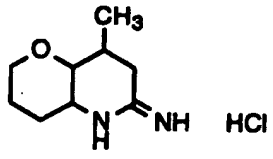
Step E: 5(6H)-Oxa-*cis*-hexahydro-quinoline-(1H)-2-one

The above compound is prepared in a similar fashion as Example 121, Step D, but substituting 1-benzyl-5(6H)-oxa-*cis*-hexahydro-quinoline-2-one in place of 1-benzyl-3-methyl-octahydro-*cis*-pyrano[4,3-b]pyridin-2-one.

Step F: 2-Imino-5(6H)-oxa-*cis*-hexahydro-(1H)-quinoline hydrochloride

The above compound is prepared from 5(6H)-oxa-*cis*-hexahydro-quinoline-(1H)-2-one following the procedures described in Steps E and F of Example 116.

EXAMPLE 161



2-Imino-4-methyl-5(6H)-oxa-*cis*-hexahydro-(1H)-quinoline hydrochloride

Step A: 1-Benzyl-4-methyl-3,4,6,7-tetrahydro-pyrindin-2,5-dione

A solution of 3-benzylamino-cyclopent-2-en-1-one (2.0 g, 10.7 mmol) and diethyl ethylidenemalonate (2.5 mL, 13.7 mmol) was stirred for 5 days at 140 °C. The cooled mixture was evaporated, and the residue partitioned between ethyl acetate and brine solution. The organic layer was evaporated, and the crude product chromatographed on silica gel (25% acetone/hexane) to afford the title compound as an oil that solidified upon standing; yield 950 mg (35%).

^{1}H NMR (400 MHz, $CDCl_3$): d 1.11 (d, 3H); 2.42 (m, 2H); 2.53-2.65 (m, 2H); 2.78 (dd, 1H); 2.92 (m, 1H); 4.79 (d, 1H); 5.07 (d, 1H); 7.18-7.37 (m, 5H).
Mass spectrum: m/e 256 (M + 1).

Step B: 1-Benzyl-4-methyl-*cis*-hexahydro-pyrindin-2,5-dione

The above compound is prepared in a similar fashion as Example 160, Step B, but substituting 1-benzyl-4-methyl-3,4,6,7-tetrahydro-pyrindin-2,5-dione in place of 1-benzyl-3,4,6,7-tetrahydro-pyrindin-2,5-dione.

Step C: 1-Benzyl-4-methyl-5-oxa-*cis*-hexahydro-quinoline-2,6-dione and 1-benzyl-4-methyl-6-oxa-*cis*-hexahydro-quinoline-2,5-dione

The above compound is prepared in a similar fashion as Example 160, Step C, but substituting 1-benzyl-4-methyl-*cis*-hexahydro-pyrindin-2,5-dione in place of 1-benzyl-*cis*-hexahydro-pyrindin-2,5-dione.

Step D: 1-Benzyl-4-methyl-5(6H)-oxa-*cis*-hexahydro-quinoline-2-one

The above compound is prepared in a similar fashion as Example 160, Step D, but substituting 1-benzyl-4-methyl-5-oxa-*cis*-

hexahydro-quinoline-2,6-dione and 1-benzyl-6-oxa-*cis*-hexahydro-quinoline-2,5-dione in place of 1-benzyl-5-oxa-*cis*-hexahydro-quinoline-2,6-dione and 1-benzyl-6-oxa-*cis*-hexahydro-quinoline-2,5-dione.

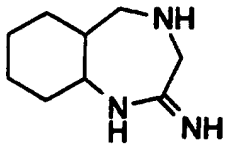
Step E: 4-Methyl-5(6H)-oxa-cis-hexahydro-quinoline-(1H)-2-one

The above compound is prepared in a similar fashion as Example 121, Step D, but substituting 1-benzyl-4-methyl-5(6H)-oxa-*cis*-hexahydro-quinoline-2-one in place of 1-benzyl-3-methyl-octahydro-*cis*-pyrano[4,3-b]pyridin-2-one.

Step F: 2-Imino-4-methyl-5(6H)-oxa-*cis*-hexahydro-(1H)-quinoline hydrochloride

The above compound is prepared from 4-methyl-5(6H)-oxa-*cis*-hexahydro-quinoline-(1H)-2-one following the procedures described in Steps E and F of Example 116.

EXAMPLE 162



2-Imino-decahydro-trans-1,4-benzo(e)diazepine dihydrochloride

Step A: (+) and (-) -cis-2-t-Butyloxycarbonylamino-cyclohexanemethanol

To a 60 mL ethanol solution of (+)-cis-2-benzylamino-cyclohexanemethanol (2 g, 9.1 mmol) was added 0.7 g of 10% Pd/C. This mixture was subjected to hydrogenolysis condition in a Parr shaker (H_2, 50 psi) overnight. Then the catalyst was removed by suction filtration through a pad of Celite. The solvent was removed under

reduced pressure and the residue was dissolved in 60 mL of acetonitrile. To it was added 11 mL of 1N NaOH and 2.39 g (11 mmol) of di-t-butyl dicarbonate. After stirring overnight, the solvent was removed under reduced pressure. Resulting oil was chromatoghaphed on silica gel eluting with hexanes/EtOAc to obtain 1.98 g of (+) -cis-2-t-butyloxycarbonylamino-cyclohexanemethanol. (-) -cis-2-t-Butyloxycarbonylamino-cyclohexanemethanol was obtained in a similar fashion starting from (-)-cis-2-benzylamino-cyclohexanemethanol.

^{1}H-NMR (500 MHz, $CDCl_3$): d 4.8(br s, 1H), 4.2(br s, 1H), 4.05(br s, 1H), 3.4-3.2(m, 2H), 1.8-0.8(m, 17H).

Step B: cis-2-tButyloxycarbonyl-aminocyclohexanecarboxaldehyde

To a 60 mL dry dichloromethane solution of dimethylsulfoxide (1.86 mL, 26.2 mmol) was added oxalyl chloride (1.14 mL, 13.0 mmol) with cooling in a dryice-acetone bath. After stirring for 15 min, a solution of 1 g (4.36 mmol) of (+) -2-t-butyloxycarobonylamino-cyclohexanemethanol and (-) -2-t-butyloxycarbonylamino-cyclohexanemethanol (1 g, 4.36 mmol) in 30 mL of CH2Cl2 was added with a cannula. The internal temperature was maintained between -50 and -60 °C for 35min and the reaction was quenched by addition of 4.86 mL (34.8mmol) of Et3N . The cooling bath was removed and the reaction mixture was warmed up to room temperature. The solvent was removed under reduced pressure and the residue was diluted with EtOAc and water. The phases were separated and the aqueous phase was extracted twice with small portions of EtOAc. The combined organic phases were dried over anhydrous Na2SO4, filtered, concentrated and chromatographed on silca gel eluting with hexanes/EtOAc to obtain 2.0 g of the title compound.

^{1}H-NMR (500 MHz, $CDCl_3$): d 9.71 (s, 1H), 5.23 (br.s, 1H), 3.98 (br s, 1H), 2.7 (br s, 1H), 2.0-1.2 (m., 17H).

Step C: cis/trans-2-t-Butyloxycarbonylamino-cyclohexanecarboxaldehyde

(+/-) -cis-2-t-Butyloxycarobonylamino-cyclohexanecarboxaldehyde (2 g, 8.8 mmol) was dissolved in 100 mL of methanol. To it was added NaOMe/MeOH prepared from 10 mg sodium and 5 mL of dry methanol. This mixture was heated to reflux for 2 h then 47mg of NH4Cl was added and the solvent was removed under reduced pressure. The residue was chromatoghaphed on silica gel eluting with hexanes/EtOAc to obtain 1.7 g of the title compound. The ratio of cis and trans isomers was determined to be 1 : 3.2 (cis/trans) by ^{1}H-NMR.

^{1}H-NMR for (+/-) -trans-2-t-Butyloxycarbonylamino-cyclohexanecarboxaldehyde (500 MHz, CDCl3): d 9.6 (s, 1H), 4.5 (br s, 1H), 3.8 (br.s, 1H), 2.05-1.2 (m, 17H).

Step D: N-(cis/trans-(2-t-Butyloxycarbonylamino-cyclohexyl)methyl)-glycine methyl ester

To a 75 mL dry methanol solution of (+/-) -cis/trans-2-t-butyloxycarbonylamino-cyclohexanecarboxaldehyde (1.7 g, 7.5 mmol) were added glycine methylester hydrochloride (1.13 g, 9 mmol) and 3 g of powedered molecular sieves (3A). After stirring overnight, a THF (50 mL) solution of 1.4 g (22.3 mmol) of sodiumcyanoborohydride was added. This mixture was stirred for 8 h and the solvent was removed under reduced pressure. The residue was suspended in EtOAc and was filtered through a pad of Celite. The filtrate was washed with sat. NaHCO3, dried with anhydrous Na2SO4, filtered, concetrated and chromatographed on silica gel eluting with hexanes/EtOAc followed by CH2Cl2/MeOH to obtain 600 mg of the desired compound.

^{1}H-NMR (500MHz, CDCl3): d 3.73 (s, 3H), 1.45 (s, 9H) other peaks could not be analyzed due to the broadning .

Mass Spectrum: m/e = 301 (M+1).

Step E: N-(cis/trans-(2-amino-cyclohexyl)methyl)-glycine methyl ester

To a 10 mL EtOAc solution of (+/-)-N-(cis/trans-(2-t-butyloxycarbonylamino-cyclohexyl)methyl)-glycine methyl ester (300 mg, 1.0mmol) was added 10 mL of EtOAc saturated with anhydrous HCl gas. After stirring for 2 h, the solvent was removed under reduced pressure to give a white solid. This material was chromatographed on silica gel eluing with $CHCl_3$:MeOH:NH_4OH (40:10:1) to obtain 180 mg of the desired product.

^{1}H-NMR (500 MHz, $CDCl_3$): d 3.75 (s, 3H), 3.05-2.95 (m, 3H), 2.4-2.3 (m, 2H).

Mass Spectrum: m/e = 201(M+1).

Step F: 4-t-Butyloxycarbonyl-octahydro-1H-benzo(e)-cis/trans1,4-diazepine-2(3H)-one

To a 10 mL absolute ethanol solution of (+/-)-N-(cis/trans-(2-amino-cyclohexyl)methyl)-glycine methyl ester (180 mg, 0.90 mmol) was added 186 mg (1.35 mmol) of potassium carbonate. This slurry was heated to reflux overnight. TLC analysis of the reaction indicated that the starting material disappeared and a product was formed. Then the solvent was removed under reduced pressure. Resuting material was dissolved in 10 mL of acetonitrile and 2 mL of water, to which was added 254 mg (1.16 mmol) of di-t-butyldicarbonate. After stirring overnight, acetonitrile was removed under reduced pressure and the residue was diluted with EtOAc and saturated ammonium chloride solution. The organic phase was separated and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over anhydrous Na2SO4, filtered, concentrated and chromatographed on silica gel eluting with CH2Cl2/MeOH to obtain 146 mg of the desired compound.

^{1}H NMR (500 MHz, $CDCl_3$): d5.3 (br.s, 2H), 4.2-3.6 (br m, 4H), 3.05 (br s, 1H), 2.8 (br s, 1H), 1.47 (s, 9H).

Mass Spectrum: m/e = 269 (M+1).

Step G: 4-t-Butyloxycarbonyl-2-imino-decahydro-1H-benzo(e)-trans-1,4-diazepine

This compounds were prepared following the procedure of EXAMPLE 43 Step E and F. The cis and trans isomers were separated by silica gel chromatography eluting with CHCl3:MeOH:NH4OH (40:5:1).

^{1}H-NMR (500 MHz, $CDCl_3$): d4.7 (m, 1H), 4.2-3.6 (m, 5H), 3.05 (br s, 1H), The rest of the spectum could not be analyzed due to line broadning.

Mass Spectrum: m/e = 268 (M+1).

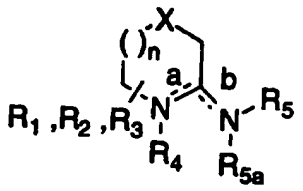
Step H: 2-Imino-decahydro-trans-1,4-benzo(e)diazepine dihydrochloride

Title compound was prepared as described in Example 156 Step F.

Mass Spectrum: m/e = 168(M+1).

WHAT IS CLAIMED IS:

1. A compound of Formula I



I

or a pharmaceutically acceptable salt thereof wherein:
side a or side b has a double bond,
n is 0, 1, 2, 3 or 4
X is selected from CH_2, $CR_{12}R_{13}$, O, S(O)m, NH, and -N(C_{1-6}alkyl)-,
m is 0, 1 or 2,
R_1, R_2, R_3, R_{12} and R_{13} are each independently selected from the group consisting of

(a) hydrogen,
(b) C_{1-12}alkoxy,
(c) C_{1-12}alkylS(O)k wherein k is 0, 1 or 2,
(d) mono C_{1-12}alkylamino,
(e) (di-C_{1-12}alkyl)amino,
(f) C_{1-12}alkylcarbonyl,
(g) C_{1-12}alkyl,
(h) C_{2-12}alkenyl,
(i) C_{2-12}alkynyl,
(j) C_{5-10}cycloalkyl,
(k) hetero C_{5-10}cycloalkyl,wherein the hetero C_{5-10}cycloalkyl optionally contains 1 or 2 heteroatoms selected from S, O and N,
(l) aryl, selected from phenyl or naphthyl,
(m) heteroaryl, wherein heteroaryl is selected from the group consisting of:
    (1) benzimidazolyl,
    (2) benzofuranyl,

(3) benzooxazolyl,
(4) furanyl,
(5) imidazolyl,
(6) indolyl,
(7) isooxazolyl,
(8) isothiazolyl,
(9) oxadiazolyl,
(10) oxazolyl,
(11) pyrazinyl,
(12) pyrazolyl,
(13) pyridyl,
(14) pyrimidyl,
(15) pyrrolyl,
(17) isoquinolyl,
(18) tetrazolyl,
(19) thiadiazolyl,
(20) thiazolyl,
(21) thienyl, and
(22) triazolyl,

(n) amino,
(o) oxo,
(p) C(O)OH,
(q) C(O)OR6, R6 is selected from hydrogen, phenyl, cyclohexyl or C_{1-6}alkyl,

each of (b) to (m) being optionally mono or di- substituted the substituents being independently selected from
(1) hydroxy,
(2) carboxy,
(3) -NR6R7, where R7 is selected from hydrogen, phenyl, cyclohexyl or C_{1-6}alkyl,
(4) -OR6,
(5) -C(O)OR6,
(6) -S(O)kR6,
(7) halo selected from F, Cl, Br and I,

(8) -C(=NR6)-NHR7,
(9)-S-C(=NR6)-NHR7,

(r) hydroxy,

or when two members of the group R1, R2 and R3 including the optional substituents present thereon, reside on the same atom of Formula I, or two of the group R1, R2 and R3, including the optional substituents present thereon, reside on adjacent atoms of Formula I, said two members may optionally be joined, such that together with the atoms to which they are attached there is formed a saturated or unsaturated monocyclic ring of 5, 6 or 7 atoms, said monocyclic ring optionally containing up to three hetero atoms selected from N, O or S,

or when a member of the group R1, R2 and R3 including the optional substituents present thereon, resides on an atom adjacent to the N on which R4 resides, said member may optionally be joined with R4, such that together with the N on which R4 resides and the carbon on which said member resides there is formed a saturated or unsaturated monocyclic heterocycle of 5, 6 or 7 atoms, said monocycle optionally containing up to three hetero atoms selected from N, O or S,

with the proviso that one of R12 and R13 are other than H,

R4, R5 and R5a are each independently selected from the group consisting of

(a) hydrogen,

(b) linear and branched C1-12alkyl, optionally mono or di-substituted, the substituents being independently selected from

(1) hydroxy,
(2) carboxy,
(3) -NR6R7,
(4) -OR6,
(5) -C(O)OR6,

(6) -S(O)$_k$R$_6$,
(7) halo selected from F, Cl, Br and I,
(8) phenyl, optionally mono or di-substituted with hydroxy, halo, C$_{1-4}$alkyl, or C$_{1-4}$alkoxy,

(c) -C(O)NR$_8$R$_9$, where R$_8$ and R$_9$ are each independently hydrogen, phenyl, cyclohexyl or C$_{1-6}$alkyl, said C$_{1-6}$alkyl optionally substituted by
(1) hydroxy,
(2) amino,
(3) carboxy,
(4) -NR$_{10}$R$_{11}$, wherein R$_{10}$ and R$_{11}$ are each independently H, C$_{1-6}$alkyl, phenyl or benzyl,
(5) -OR$_{10}$,
(6) -C(O)OR$_{10}$,
(7) -S(O)$_m$R$_{10}$, where m is 0, 1 or 2,
(8) halo selected from F, Cl, Br and I,
(9) optionally substituted aryl wherein aryl and aryl substituents are as defined above,
(10) optionally substituted heteroaryl wherein heteroaryl and heteroaryl substituents are as defined above,
(11) optionally substituted C5-10cycloalkyl wherein cycloalkyl and cycloalkyl substituents are as defined above,
(12) optionally substituted hetero C$_{5-10}$cycloalkyl wherein hetero cycloalkyl and hetero cycloalkyl substituents are as defined above,

(d) -C(S)NR$_8$R$_9$,
(e) -C(O)R$_9$,
(f) -C(O)OR$_9$,
(g) -C(S)R$_9$,
(h) phenyl,
(i) cyclohexyl,

provided that R$_4$ is present only when side a is a single bond and R5a is present only when side b is a single bond.

2. A compound according to claim 1 wherein
n is 0, 1, 2, 3 or 4,
X is selected from CH_2, $CR_{12}R_{13}$, O, $S(O)_m$, NH, and -N(C_{1-6}alkyl)-,
m is 0, 1 or 2,
R_1, R_2, R_3, R_{12} and R_{13} are each independently selected from the group consisting of

(a) hydrogen,
(b) C_{1-6}alkoxy,
(c) C_{1-6}alkylamino,
(d) C_{1-6}alkylcarbonyl,
(e) C_{1-6}alkyl,
(f) C_{2-6}alkenyl,
(g) C_{2-6}alkynyl,
(h) C_5, C_6 or C_7cycloalkyl,
(i) hetero C_5, C_6 or C_7cycloalkyl,wherein the hetero C_5, C_6 or C_7cycloalkyl optionally contains 1 or 2 heteroatoms selected from S, O and N,
(j) aryl, selected from phenyl or naphthyl,
(k) heteroaryl, wherein heteroaryl is selected from the group consisting of:
(1) benzimidazolyl,
(2) benzofuranyl,
(3) benzooxazolyl,
(4) furanyl,
(5) imidazolyl,
(6) indolyl,
(7) isooxazolyl,
(8) isothiazolyl,
(9) oxadiazolyl,
(10) oxazolyl,
(11) pyrazinyl,
(12) pyrazolyl,
(13) pyridyl,
(14) pyrimidyl,

(15) pyrrolyl,
(16) quinolyl,
(17) tetrazolyl,
(18) thiadiazolyl,
(19) thiazolyl,
(20) thienyl, and
(21) triazolyl,

(l) hydroxy,

each of (b) to (k) being optionally mono or di- substituted the substituents being independently selected from

(1) hydroxy,
(2) carboxy,
(3) -NR_6R_7, where R_6 and R_7 are selected from hydrogen, phenyl, cyclohexyl or C_{1-6}alkyl,
(4) -OR_6,
(5) -$C(O)OR_6$,
(6) -$S(O)_kR_6$,
(7) halo selected from F, Cl, Br and I,
(8) -$C(=NR_6)$-NHR_7,
(9)-S-$C(=NR_6)$-NHR_7,

or when two members of the group R_1, R_2 and R_3 including the optional substituents present thereon, reside on the same atom of Formula I, or two of the group R_1, R_2 and R_3, including the optional substituents present thereon, reside on adjacent atoms of Formula I, said two members may optionally be joined, such that together with the atoms to which they are attached there is formed a saturated or unsaturated monocyclic ring of 5, 6 or 7 atoms, said monocyclic ring optionally containing up to three hetero atoms selected from N, O or S,

or when a member of the group R_1, R_2 and R_3 including the optional substituents present thereon, resides on an atom adjacent to the N on which R_4 resides, said member may optionally be joined with R_4, such that together with the N

on which R_4 resides and the carbon on which said member resides there is formed a saturated or unsaturated monocyclic heterocycle of 5, 6 or 7 atoms, said monocycle optionally containing up to three hetero atoms selected from N, O or S,

with the proviso that one of R_{12} and R_{13} is other than hydrogen,

R_4, R_5 and R_{5a} are each independently selected from the group consisting of

(a) hydrogen,

(b) linear and branched C_{1-6}alkyl, optionally mono or di-substituted, the substituents being independently selected from

(1) hydroxy,
(2) carboxy,
(3) $-NR_6R_7$,
(4) $-OR_6$,
(5) $-C(O)OR_6$,
(6) $-S(O)_kR_6$, where k is 0, 1 or 2,
(7) halo selected from F, Cl, Br and I,

(c) $-C(O)NR_8R_9$, where R_8 and R_9 are each independently hydrogen, phenyl, cyclohexyl or C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted by

(1) hydroxy,
(2) amino,
(3) carboxy,
(4) $-NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently H, C_{1-4}alkyl, phenyl or benzyl,
(5) $-OR_{10}$,
(6) $-C(O)OR_{10}$,
(7) $-S(O)_mR_{10}$, where m is 0, 1 or 2,
(8) halo selected from F, Cl, Br and I,
(9) optionally substituted aryl wherein aryl andaryl substituents are as defined above,

(10) optionally substituted heteroaryl wherein heteroaryl and heteroaryl substituents are as defined above,

(11) optionally substituted C_5, C_6 or C_7cycloalkyl wherein cycloalkyl and cycloalkyl substituents are as defined above,

(12) optionally substituted hetero C_5, C_6 or C_7cycloalkyl wherein hetero cycloalkyl and hetero cycloalkyl substituents are as defined above,

(d) -C(S)NR8R9,

(e) -C(O)R9,

(f) -C(O)OR9,

(g) -C(S)R9,

(h) phenyl,

(i) cyclohexyl,

such that R4 is present only when side a is a single bond and side b is a double bond.

3. A compound according to claim 2 wherein

n is 0, 1, 2, 3 or 4

X is selected from CH_2, $CR_{12}R_{13}$, O, NH and -N(C_{1-4}alkyl)-,

R_1, R_2, R_3, R_{12} and R_{13} are each independently selected from the group consisting of

(a) hydrogen,

(b) C_{1-6}alkoxy,

(c) C_{1-6}alkylamino,

(d) C_{1-6}alkylcarbonyl,

(e) C_{1-6}alkyl,

(f) C_{2-6}alkenyl,

(g) C_5, C_6 or C_7cycloalkyl,

(h) hetero C_5 or C_6 cycloalkyl,wherein the hetero C_5 or C_6 cycloalkyl optionally contains 1 heteroatom selected from S, O and N,

(i) aryl, selected from phenyl or naphthyl,

(j) heteroaryl, wherein heteroaryl is selected from the group consisting of:

(1) furanyl,
(2) pyrazinyl,
(3) pyrazolyl,
(4) pyridyl,
(5) pyrimidyl,
(6) thiazolyl,
(7) thienyl, and
(8) triazolyl,

(k) hydroxy,

each of (b) to (j) being optionally mono or di- substituted the substituents being independently selected from

(1) hydroxy,
(2) carboxy,
(3) $-NR_6R_7$, wherein R_6 and R_7 are each independently hydrogen or C_{1-4}alkyl,
(4) $-OR_6$,
(5) $-C(O)OR_6$,
(6) $-S(O)_kR_6$, where k is 0, 1 or 2,
(7) halo selected from F, Cl, Br and I,
(8) $-C(=NR_6)-NHR_7$,
(9) $-S-C(=NR_6)-NHR_7$,

or when two members of the group R_1, R_2 and R_3 including the optional substituents present thereon, reside on the same atom of Formula I, or two of the group R_1, R_2 and R_3, including the optional substituents present thereon, reside on adjacent atoms of Formula I, said two members may optionally be joined, such that together with the atoms to which they are attached there is formed a saturated or unsaturated monocyclic ring of 5, 6 or 7 atoms, said monocyclic ring optionally containing up to three hetero atoms selected from N, O or S,

or when a member of the group R_1, R_2 and R_3 including the optional substituents present thereon, resides on an atom adjacent to the N on which R_4 resides, said member may optionally be joined with R_4, such that together with the N on which R_4 resides and the carbon on which said member resides there is formed a saturated or unsaturated monocyclic heterocycle of 5, 6 or 7 atoms, said monocycle optionally containing up to three hetero atoms selected from N, O or S,

with the proviso that one of R_{12} and R_{13} is other than hydrogen,

R_4, R_5 and R_{5a} are each independently selected from the group consisting of

(a) hydrogen,

(b) linear and branched C_{1-6}alkyl, optionally mono or di-substituted, the substituents being independently selected from

(1) hydroxy,

(2) carboxy,

(3) $-NR_6R_7$,

(4) $-OR_6$,

(5) $-C(O)OR_6$,

(6) $-S(O)_kR_6$,

(7) halo selected from F, Cl, Br and I,

(c) $-C(O)NR_8R_9$, where R_8 and R_9 are each independently hydrogen, phenyl, cyclohexyl or C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted by

(1) hydroxy,

(2) amino,

(3) carboxy,

(4) $-NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently H, C_{1-4}alkyl, phenyl or benzyl,

(5) $-OR_{10}$,

(6) $-C(O)OR_{10}$,

(7) $-S(O)_mR_{10}$, where m is 1 or 2,

(8) halo selected from F, Cl, Br and I,
(9) optionally substituted aryl wherein aryl and aryl substituents are as defined above,
(10) optionally substituted heteroaryl wherein heteroaryl and heteroaryl substituents are as defined above,
(11) optionally substituted C_5 or C_6 cycloalkyl wherein cycloalkyl and cycloalkyl substituents are as defined above,
(12) optionally substituted hetero C_5 or C_6 cycloalkyl wherein hetero cycloalkyl and hetero cycloalkyl substituents are as defined above,

(d) $-C(S)NR_8R_9$,
(e) $-C(O)R_9$,
(f) $-C(O)OR_9$,
(g) $-C(S)R_9$,
(h) phenyl,
(i) cyclohexyl,

such that R_4 is present only when side a is a single bond and side b is a double bond.

4. A compound according to Claim 3 wherein
n is 0, 1, 2 or 3,
X is selected from $CR_{12}R_{13}$, NH and $-N(C_{1-4}alkyl)-$,
R_1, R_2, R_3, R_{12} and R_{13} are each independently selected from the group consisting of

(a) hydrogen,
(b) C_{1-4}alkoxy,
(c) C_{1-4}alkylamino,
(d) C_{1-4}alkylcarbonyl,
(e) linear and branched C_{1-4}alkyl,
(f) hydroxy,

each of (b) to (e) being optionally mono or di- substituted the substituents being independently selected from
(1) hydroxy,

(2) carboxy,
(3) -NR_6R_7, wherein R_6 and R_7 are each independently hydrogen or C_{1-3}alkyl,
(4) -OR_6,
(5) -$C(O)OR_6$,
(6) -$S(O)_kR_6$, where k is 0, 1 or 2,
(7) halo selected from F, Cl, Br and I,

or when two members of the group R_1, R_2 and R_3 including the optional substituents present thereon, reside on the same atom of Formula I, or two of the group R_1, R_2 and R_3, including the optional substituents present thereon, reside on adjacent atoms of Formula I, said two members may optionally be joined, such that together with the atoms to which they are attached there is formed a saturated or unsaturated monocyclic ring of 5, 6 or 7 atoms, said monocyclic ring optionally containing up to three hetero atoms selected from N, O or S,

or when a member of the group R_1, R_2 and R_3 including the optional substituents present thereon, resides on an atom adjacent to the N on which R_4 resides, said member may optionally be joined with R_4, such that together with the N on which R_4 resides and the carbon on which said member resides there is formed a saturated or unsaturated monocyclic heterocycle of 5, 6 or 7 atoms, said monocycle optionally containing up to three hetero atoms selected from N, O or S,

with the proviso that one of R_{12} and R_{13} is other than hydrogen,

R_4, R_5 and R_{5a} are each independently selected from the group consisting of

(a) hydrogen,
(b) -$C(O)NR_8R_9$, where R_8 and R_9 are each independently hydrogen or C_{1-3}alkyl, said C_{1-3}alkyl optionally substituted by
(1) hydroxy,

(2) amino,
(3) carboxy,
(4) -$NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently H or C_{1-3}alkyl,
(5) -OR_{10},
(6) -$C(O)OR_{10}$,
(7) -$S(O)_mR_{10}$, where m is 0, 1 or 2,
(8) halo selected from F, Cl, Br and I,

(c) -$C(S)NR_8R_9$,
(d) -$C(O)R_9$,
(e) -$C(O)OR_9$,
(f) -$C(S)R_9$,
(g) -$C(S)HR_9$.
(h) -C_{1-4}alkyl; and

R_{13} is hydrogen.

5. A compound according to Claim 4 wherein

n is 0, 1, 2 or 3,
X is selected from $CR_{12}R_{13}$, NH and -$N(C_{1-4}alkyl)$-,
R_1, R_2, R_3,R_{12} and R_{13} are each independently selected from the group consisting of

(a) hydrogen,
(b) C_{1-4}alkoxy,
(c) C_{1-4}alkylamino,
(d) C_{1-4}alkylcarbonyl,
(e) linear and branched C_{1-4}alkyl,
(f) hydroxy,

each of (b) to (e) being optionally mono or di- substituted the substituents being independently selected from
(1) hydroxy,
(2) carboxy,
(3) -NR_6R_7, wherein R6 and R7 are each independently hydrogen or C_{1-3}alkyl,

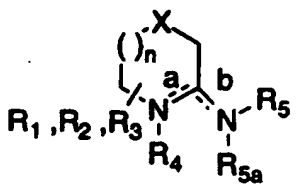
(4) -OR_6,
(5) -$C(O)OR_6$,
(6) -$S(O)_kR_6$, where k is 0, 1 or 2,
(7) halo selected from F, Cl, Br and I,

R_4 is selected from the group consisting of
(a) hydrogen,
(b) -C(O)NHR9, where R9 is hydrogen or C_{1-3}alkyl, said C_{1-3}alkyl optionally substituted by
(1) hydroxy,
(2) amino,
(3) carboxy,
(4) -$NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently C_{1-3}alkyl,
(5) -OR_{10},
(6) -$C(O)OR_{10}$,
(7) -$S(O)_mR_{10}$, where m is 1 or 2,
(8) halo selected from F, Cl, Br and I,
(c) -C(S)NHR9;
(d) -C1-4alkyl.

R_5 is selected from the group consisting of
(a) hydrogen,
(b) -C(O)NHR9,
(c) -C(S)NR8R9.
(d) -C_{1-4}alkyl, and

R_{5a} and R_{13} are each hydrogen.

6. A compound of Formula I according to Claim 1



I

or pharmaceutically acceptable salts thereof wherein
side a or side b has a double bond,
n is 0, 1, 2, 3 or 4
X is selected from CH_2, O, $S(O)_m$ and NH,
R_1, R_2 and R_3 are each independently selected from the group consisting of

(a) hydrogen,
(b) C_{1-12}alkoxy,
(c) C_{1-12}alkyl$S(O)_k$ wherein k is 0, 1 or 2,
(d) mono C_{1-12}alkylamino,
(e) (di-C_{1-12}alkyl)amino,
(f) C_{1-12}alkylcarbonyl,
(g) C_{1-12}alkyl,
(h) C_{2-12}alkenyl,
(i) C_{2-12}alkynyl,
(j) C_{5-10}cycloalkyl,
(k) hetero C_{5-10}cycloalkyl,wherein the hetero C_{5-10}cycloalkyl optionally contains 1 or 2 heteroatoms selected from S, O and N,
(l) aryl, selected from phenyl or naphthyl,
(m) heteroaryl, wherein heteroaryl is selected from the group consisting of:
(1) benzimidazolyl,
(2) benzofuranyl,
(3) benzooxazolyl,
(4) furanyl,
(5) imidazolyl,
(6) indolyl,
(7) isooxazolyl,
(8) isothiazolyl,
(9) oxadiazolyl,
(10) oxazolyl,
(11) pyrazinyl,
(12) pyrazolyl,

(13) pyridyl,
(14) pyrimidyl,
(15) pyrrolyl,
(17) isoquinolyl,
(18) tetrazolyl,
(19) thiadiazolyl,
(20) thiazolyl,
(21) thienyl, and
(22) triazolyl,

(n) amino,
(o) oxo,
(p) C(O)OH,
(q) C(O)OR6, R6 is selected from hydrogen, phenyl, cyclohexyl or C1-6alkyl,

each of (b) to (m) being optionally mono or di- substituted the substituents being independently selected from
(1) hydroxy,
(2) carboxy,
(3) -NR6R7, where R7 is selected from hydrogen, phenyl, cyclohexyl or C1-6alkyl,
(4) -OR6,
(5) -C(O)OR6,
(6) -S(O)kR6,
(7) halo selected from F, Cl, Br and I,
(8) -C(=NR6)-NHR7,
(9)-S-C(=NR6)-NHR7,

or when two members of the group R1, R2 and R3 including the optional substituents present thereon, reside on the same atom of Formula I, or two of the group R1, R2 and R3, including the optional substituents present thereon, reside on adjacent atoms of Formula I, said two members may optionally be joined, such that together with the atoms to which they are attached there is formed a saturated or unsaturated monocyclic ring of 5, 6 or 7 atoms, said

monocyclic ring optionally containing up to three hetero atoms selected from N, O or S,

or when a member of the group R_1, R_2 and R_3 including the optional substituents present thereon, resides on an atom adjacent to the N on which R_4 resides, said member may optionally be joined with R_4, such that together with the N on which R_4 resides and the carbon on which said member resides there is formed a saturated or unsaturated monocyclic heterocycle of 5, 6 or 7 atoms, said monocycle optionally containing up to three hetero atoms selected from N, O or S,

R_4, R_5 and R_{5a} are each independently selected from the group consisting of

(a) hydrogen,

(b) linear and branched C_{1-12}alkyl, optionally mono or di-substituted, the substituents being independently selected from

(1) hydroxy,
(2) carboxy,
(3) $-NR_6R_7$,
(4) $-OR_6$,
(5) $-C(O)OR_6$,
(6) $-S(O)_kR_6$,
(7) halo selected from F, Cl, Br and I,
(8) phenyl, optionally mono or di-substituted with hydroxy, halo, C_{1-4}alkyl, or C_{1-4}alkoxy,

(c) $-C(O)NR_8R_9$, where R_8 and R_9 are each independently hydrogen, phenyl, cyclohexyl or C_{1-6}alkyl, said C_{1-6}alkyl optionally substituted by

(1) hydroxy,
(2) amino,
(3) carboxy,
(4) $-NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently H, C_{1-6}alkyl, phenyl or benzyl,

(5) -OR_{10},
(6) -$C(O)OR_{10}$,
(7) -$S(O)_mR_{10}$, where m is 0, 1 or 2,
(8) halo selected from F, Cl, Br and I,
(9) optionally substituted aryl wherein aryl and aryl substituents are as defined above,
(10) optionally substituted heteroaryl wherein heteroaryl and heteroaryl substituents are as defined above,
(11) optionally substituted C5-10cycloalkyl wherein cycloalkyl and cycloalkyl substituents are as defined above,
(12) optionally substituted hetero C_{5-10}cycloalkyl wherein hetero cycloalkyl and hetero cycloalkyl substituents are as defined above,

(d) -$C(S)NR_8R_9$,
(e) -$C(O)R_9$,
(f) -$C(O)OR_9$,
(g) -$C(S)R_9$,
(h) phenyl,
(i) cyclohexyl,

provided that R_4 is present only when side a is a single bond and R5a is present only when side b is a single bond.

7. A compound according to Claim 6 wherein
n is 0, 1, 2, 3 or 4,
X is selected from CH_2, O, S and NH,
R_1, R_2 and R_3 are each independently selected from the group consisting of

(a) hydrogen,
(b) C_{1-6}alkoxy,
(c) C_{1-6}alkylamino,
(d) C_{1-6}alkylcarbonyl,
(e) C_{1-6}alkyl,
(f) C_{2-6}alkenyl,

(g) C_5, C_6 or C_7cycloalkyl,

(h) hetero C_5 or C_6 cycloalkyl,wherein the hetero C_5 or C_6 cycloalkyl optionally contains 1 heteroatom selected from S, O and N,

(i) aryl, selected from phenyl or naphthyl,

(j) heteroaryl, wherein heteroaryl is selected from the group consisting of:

(1) furanyl,
(2) pyrazinyl,
(3) pyrazolyl,
(4) pyridyl,
(5) pyrimidyl,
(6) thiazolyl,
(7) thienyl, and
(8) triazolyl,

each of (b) to (j) being optionally mono or di- substituted the substituents being independently selected from

(1) hydroxy,
(2) carboxy,
(3) -NR_6R_7, where R_6 and R_7 are each independently hydrogen, phenyl or C_{1-4}alkyl,
(4) -OR_6,
(5) -$C(O)OR_6$,
(6) -$S(O)_kR_6$, where k is 0, 1 or 2,
(7) halo selected from F, Cl, Br and I,

or when two members of the group R_1, R_2 and R_3 including the optional substituents present thereon, reside on the same atom of Formula I, or two of the group R_1, R_2 and R_3, including the optional substituents present thereon, reside on adjacent atoms of Formula I, said two members may optionally be joined, such that together with the atoms to which they are attached there is formed a saturated or unsaturated monocyclic ring of 5, 6 or 7 atoms, said

monocyclic ring optionally containing up to three hetero atoms selected from N, O or S,

or when a member of the group R_1, R_2 and R_3 including the optional substituents present thereon, resides on an atom adjacent to the N on which R_4 resides, said member may optionally be joined with R_4, such that together with the N on which R_4 resides and the carbon on which said member resides there is formed a saturated or unsaturated monocyclic heterocycle of 5, 6 or 7 atoms, said monocycle optionally containing up to three hetero atoms selected from N, O or S,

R_4, R_5 and R_{5a} are each independently selected from the group consisting of

(a) hydrogen,

(b) linear and branched C_{1-6}alkyl, optionally mono or di-substituted, the substituents being independently selected from

(1) hydroxy,
(2) carboxy,
(3) $-NR_6R_7$,
(4) $-OR_6$,
(5) $-C(O)OR_6$,
(6) $-S(O)_kR_6$, where k is 0, 1 or 2,
(7) halo selected from F, Cl, Br and I,

(c) $-C(O)NR_8R_9$, where R_8 and R_9 are each independently hydrogen, phenyl, cyclohexyl or C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted by

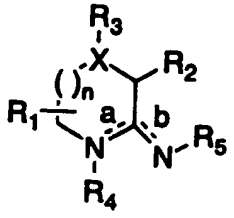
(1) hydroxy,
(2) amino,
(3) carboxy,
(4) $-NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently H, C_{1-4}alkyl, phenyl or benzyl,
(5) $-OR_{10}$,
(6) $-C(O)OR_{10}$,

(7) -S(O)mR10, where m is 0, 1 or 2,
(8) halo selected from F, Cl, Br and I,
(9 optionally substituted aryl wherein the aryl and substituents are as defined above,
(10) optionally substituted heteroaryl wherein the heteroaryl and substituents are as defined above,
(11) optionally substituted C5 or C6 cycloalkyl wherein the cycloalkyl and substituents are as defined above,
(12) optionally substituted hetero C5 or C6 cycloalkyl wherein the hetero cycloalkyl and substituents are as defined above,

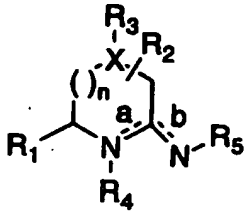
(d) -C(S)NR8R9,
(e) -C(O)R9,
(f) -C(O)OR9,
(g) -C(S)R9,
(h) phenyl,
(i) cyclohexyl,

such that R4 is present only when side a is a single bond and side b is a double bond.

8. A compound according to Claim 6 of the formula



or



wherein
n is 0, 1 or 2.

9. A compound according to Claim 8 wherein
n is 0, 1 or 2,
X is selected from CH_2 and NH,

R_1, R_2 and R_3 are each independently selected from the group consisting of

(a) hydrogen,

(b) linear and branched C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally mono or di- substituted the substituents being independently selected from

(1) carboxy,

(2) -NHR7, wherein R_6 and R_7 are each independently hydrogen or C_{1-3}alkyl,

(3) -OR_6,

(4) -$C(O)OR_6$,

(5) -$S(O)_kR_6$, where k is 0, 1 or 2,

(c) hydroxy,

(d) C_{1-6}alkoxy;

R_4 is selected from the group consisting of

(a) hydrogen,

(b) -C(O)NHR9, where R9 is hydrogen or C_{1-3}alkyl, said C_{1-3}alkyl optionally substituted by

(1) hydroxy,

(2) amino,

(3) carboxy,

(4) -$NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently C_{1-3}alkyl,

(5) -OR_{10},

(6) -$C(O)OR_{10}$,

(7) -$S(O)_mR_{10}$, where m is 0, 1 or 2,

(8) halo selected from F, Cl, Br and I,

(c) -C(S)NHR9;

(d) C_{1-3}alkyl;

R_5 are each independently selected from the group consisting of

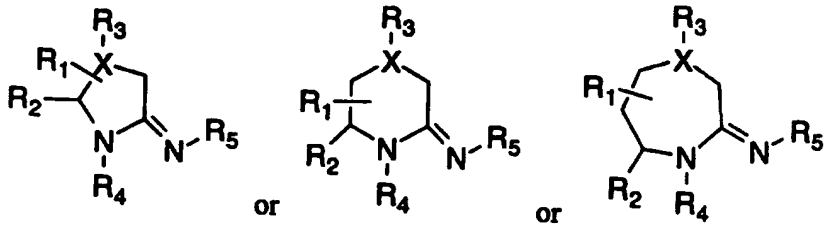
(a) hydrogen,

(b) -C(O)NHR9,

(c) -C(S)NR8R9.

(d) -C_{1-3}alkyl.

10. A compound according to Claim 9 of the formulae



wherein

X is selected from CH_2, NH and S,

R_1, R_2 and R_3 are each independently selected from the group consisting of

(a) hydrogen,

(b) linear and branched C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally mono or di- substituted the substituents being independently selected from

(1) carboxy,

(2) -NHR_7, wherein R_6 and R_7 are each independently hydrogen or C_{1-3}alkyl,

(3) -OR_6,

(4) -$C(O)OR_6$,

(5) -$S(O)_kR_6$, where k is 0, 1 or 2,

(c) hydroxy,

(d) C_{1-6}alkoxy;

R_4 is selected from the group consisting of

(a) hydrogen,

(b) -$C(O)NHR_9$, where R_9 is hydrogen or C_{1-3}alkyl, said C_{1-3}alkyl optionally substituted by

(1) hydroxy,

(2) amino,

(3) carboxy,

(4) -$NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently C_{1-3}alkyl,

(5) -OR_{10},
(6) -$C(O)OR_{10}$,
(7) -$S(O)_mR_{10}$, where m is 0, 1 or 2,
(8) halo selected from F, Cl, Br and I,

(c) -$C(S)NHR_9$;
(d) C_{1-3}alkyl;

R_5 are each independently selected from the group consisting of

(a) hydrogen,
(b) -$C(O)NHR_9$,
(c) -$C(S)NR_8R_9$.
(d) -C_{1-3}alkyl.

11. A compound according to Claim 10 wherein X is CH_2,

R_1, R_2 and R_3 are each independently is selected from the group consisting of

(a) hydrogen,
(b) linear and branched C_{1-6}alkyl, said C_{1-6}alkyl being optionally mono or di- substituted the substituents being independently selected from
(1) carboxy,
(2) -NHR_7, wherein R_6 and R_7 are each independently hydrogen or C_{1-3}alkyl,
(3) -$C(O)R_6$, and
(4) -$S(O)_kR_6$, where k is 1 or 2,
(c) hydroxy,
(d) C_{1-6}alkoxy;

R_4 is selected from the group consisting of

(a) hydrogen,
(b) C_{1-3}alkyl;

R_5 is selected from the group consisting of

(a) hydrogen,
(b) -$C(O)NHR_9$, where R_9 is hydrogen or C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted by

(1) hydroxy,
(2) amino,
(3) carboxy,
(4) -$NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently
C_{1-3}alkyl,
(5) -OR_{10},
(6) -$C(O)OR_{10}$,
(7) -SR_{10}, and
(8) -$S(O)_mR_{10}$, where m is 1 or 2,
(9) halo selected from F, Cl, Br and I,

(c) -$C(S)NR_8R_9$.

(d) C_{1-3}alkyl.

12. A compound according to Claim 11 wherein
X is CH_2,
R_1 and R_2 are each selected from the group consisting of
hydrogen, hydroxy or linear and branched C_{1-6}alkyl, said C_{1-6}alkyl
being optionally mono or di- substituted the substituents being independently selected from
(1) carboxy,
(2) -NHR_7, wherein R_6 and R_7 are each independently hydrogen or C_{1-3}alkyl,
(3) -$C(O)OR_6$, and
(4) -$S(O)_kR_6$, where k is 1 or 2,
R_3 is linear and branched C_{1-4}alkyl,
R_4 is selected from the group consisting of

(a) hydrogen,

(b) C_{1-3}alkyl;

R_5 is selected from the group consisting of

(a) hydrogen,

(b) -$C(O)NHR_9$, where R_9 is hydrogen or C_{1-4}alkyl, said

C_{1-4}alkyl optionally substituted by
(1) hydroxy,
(2) amino,
(3) carboxy,
(4) -$NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently
C_{1-3}alkyl,
(5) -OR_{10},
(6) -$C(O)OR_{10}$,
(7) -SR_{10}, and
(8) -$S(O)_mR_{10}$, where m is 1 or 2,
(9) halo selected from F, Cl, Br and I,
(c) -$C(S)NR_8R_9$.
(d) C_{1-3}alkyl.

13. Acompound according to Claim 10 wherein
X is -N-,
R_1, R_2 and R_3 are each independently is selected from the group consisting of
(a) hydrogen,
(b) linear and branched C_{1-6}alkyl, said C_{1-6}alkyl being optionally mono or di- substituted the substituents being independently selected from
(1) carboxy,
(2) -NHR_7, wherein R_6 and R_7 are each independently hydrogen or C_{1-3}alkyl,
(3) -$C(O)OR_6$, and
(4) -$S(O)_kR_6$, where k is 1 or 2,
(c) hydroxy,
(d) C_{1-6}alkoxy;
R_4 is selected from the group consisting of
(a) hydrogen,
(b) C_{1-3}alkyl;
R_5 is selected from the group consisting of

(a) hydrogen,
(b) -C(O)NHR9, where R9 is hydrogen or C1-4alkyl, said C1-4alkyl optionally substituted by
(1) hydroxy,
(2) amino,
(3) carboxy,
(4) -NR10R11, wherein R10 and R11 are each independently C1-3alkyl,
(5) -OR10,
(6) -C(O)OR10,
(7) -SR10, and
(8) -S(O)mR10, where m is 1 or 2,
(9) halo selected from F, Cl, Br and I,
(c) -C(S)NHR9.
(d) C1-3alkyl.

14. A compound according to Claim 13

wherein
X is -N-,
R1 and R2 are each selected from
hydrogen, hydroxy or linear and branched C1-4alkyl, said C1-4alkyl being optionally mono or di- substituted the substituents being independently selected from
(1) carboxy,
(2) -NHR7, wherein R6 and R7 are each independently hydrogen or C1-3alkyl,
(3) -C(O)OR6, and
(4) -S(O)kR6, where k is 1 or 2,
R3 is methyl,
R4 is selected from the group consisting of
(a) hydrogen,

(b) C_{1-3}alkyl;

R_5 is selected from the group consisting of

(a) hydrogen,

(b) -C(O)NHR9, where R9 is hydrogen or C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted by

(1) hydroxy,

(2) amino,

(3) carboxy,

(4) $-NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently C_{1-3}alkyl,

(5) $-OR_{10}$,

(6) $-C(O)OR_{10}$,

(7) $-SR_{10}$, and

(8) $-S(O)_mR_{10}$, where m is 1 or 2,

(9) halo selected from F, Cl, Br and I,

(c) -CSNHR9.

(d) C_{1-3}alkyl.

15. Acompound according to Claim 10 wherein

X is S,

R_1 and R_2 are each independently is selected from the group consisting of

(a) hydrogen,

(b) linear and branched C_{1-6}alkyl, said C_{1-6}alkyl being optionally mono or di- substituted the substituents being independently selected from

(1) carboxy,

(2) $-NHR_7$, wherein R_6 and R_7 are each independently hydrogen or C_{1-3}alkyl,

(3) $-C(O)OR_6$, and

(4) $-S(O)_kR_6$, where k is 1 or 2,

(c) hydroxy,

(d) C_{1-6}alkoxy;

R4 is selected from the group consisting of

(a) hydrogen,

(b) C_{1-3}alkyl;

R5 is selected from the group consisting of

(a) hydrogen,

(b) -C(O)NHR9, where R9 is hydrogen or C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted by

(1) hydroxy,

(2) amino,

(3) carboxy,

(4) $-NR_{10}R_{11}$, wherein R_{10} and R_{11} are each independently

C_{1-3}alkyl,

(5) $-OR_{10}$,

(6) $-C(O)OR_{10}$,

(7) $-SR_{10}$, and

(8) $-S(O)_mR_{10}$, where m is 1 or 2,

(9) halo selected from F, Cl, Br and I,

(c) -C(S)NHR9.

(d) C_{1-3}alkyl.

16. A compound according to Claim 15

wherein

X is S,

R_1 and R_2 are each independently selected from

hydrogen, hydroxy or linear and branched C_{1-6}alkyl, said C_{1-6}alkyl

being optionally mono or di- substituted the substituents being independently selected from

(1) carboxy,

(2) -NHR7, wherein R6 and R7 are each independently hydrogen or C_{1-3}alkyl,

(3) $-C(O)OR_6$, and

(4) -S(O)$_k$R$_6$, where k is 1 or 2,

R$_4$ is selected from the group consisting of

(a) hydrogen,

(b) C$_{1-3}$alkyl;

R$_5$ is selected from the group consisting of

(a) hydrogen,

(b) -C(O)NHR$_9$, where R$_9$ is hydrogen or C$_{1-4}$alkyl, said C$_{1-4}$alkyl optionally substituted by

(1) hydroxy,

(2) amino,

(3) carboxy,

(4) -NR$_{10}$R$_{11}$, wherein R$_{10}$ and R$_{11}$ are each independently C$_{1-3}$alkyl,

(5) -OR$_{10}$,

(6) -C(O)OR$_{10}$,

(7) -SR$_{10}$, and

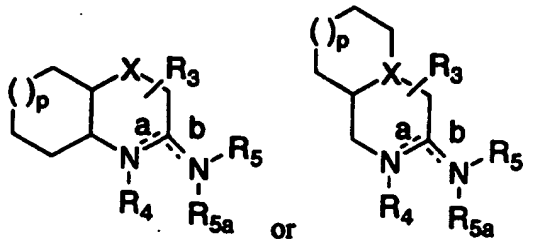
(8) -S(O)$_m$R$_{10}$, where m is 1 or 2,

(9) halo selected from F, Cl, Br and I,

(c) -CSNHR$_9$.

(d) C$_{1-3}$alkyl.

17. A compound according to Claim 6 of the formulae



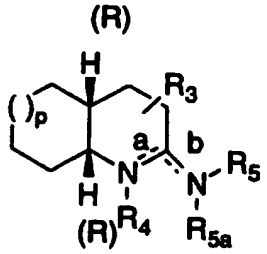
wherein p is 0, 1 or 2; and

R$_3$ and the ring formed by the joining of R$_1$ and R$_2$ are optionally mono or di-substituted with substituents selected from the group consisting of

(1) hydroxy,

(2) carboxy,
(3) -NR6R7, where R6 and R7 are each selected from hydrogen, phenyl, cyclohexyl or C1-6alkyl,
(4) -OR6,
(5) -C(O)OR6,
(6) -S(O)kR6,
(7) halo selected from F, Cl, Br and I,
(8) -C(=NR6)-NHR7,
(9)-S-C(=NR6)-NHR7.

18. A compound according to Claim 17 having cis stereochemistry at the ring junction, said compound having the formula



wherein p is 1 or 2, and
R3 and the ring formed by the joining of R1 and R2 are optionally mono or di-substituted with substituents selected from the group consisting of
(1) hydroxy,
(2) carboxy,
(3) -NR6R7, where R6 and R7 are each selected from hydrogen, phenyl, cyclohexyl or C1-6alkyl,
(4) -OR6,
(5) -C(O)OR6,
(6) -S(O)kR6,
(7) halo selected from F, Cl, Br and I,
(8) -C(=NR6)-NHR7,
(9)-S-C(=NR6)-NHR7.

19. A compound according to Claim 18 wherein

R3 is selected from

hydrogen, hydroxy or linear and branched C_{1-4}alkyl, said C_{1-4}alkyl,

optionally mono or di- substituted the substituents being independently selected from

(1) carboxy,

(2) -NHR7, wherein R6 and R7 are each independently hydrogen or C_{1-3}alkyl,

(3) -C(O)OR6, and

(4) -S(O)$_k$R6, where k is 1 or 2;

R4 is selected from the group consisting of

(a) hydrogen,

(b) C_{1-3}alkyl;

R5 is selected from the group consisting of

(a) hydrogen,

(b) -C(O)NHR9, where R9 is hydrogen or C_{1-4}alkyl, said C_{1-4}alkyl optionally substituted by

(1) hydroxy,

(2) amino,

(3) carboxy,

(4) -NR10R11, wherein R10 and R11 are each independently

C_{1-3}alkyl,

(5) -OR10,

(6) -C(O)OR10,

(7) -SR10, and

(8) -S(O)$_m$R10, where m is 1 or 2,

(9) halo selected from F, Cl, Br and I,

(c) -C(S)NR8R9.

(d) C_{1-3}alkyl.

20. A compound of Claim 1 selected from

(aa) 1-Aza-2-imino-cyclopentane hydrochloride,

(ab) 1-Aza-2-imino-3-methylcyclopentane hydrochloride,

(ac) 1-Aza-2-imino-5-methylcyclopentane hydrochloride,
(ad) 1-Aza-2-methylamino-1-cyclopentene hydrochloride,
(ae) 1-Aza-2-ethylamino-1-cyclopentene hydrochloride,
(af) 1-Aza-2-benzylamino-1-cyclopentene hydrochloride,
(ag) 1-Aza-2-cyclohexylamino-1-cyclopentene hydrochloride,
(ah) 1-Aza-2-methoxycarbonylmethylamino-1-cyclopentene hydrochloride,
(ai) 1-Aza-2-((3,4-dihydroxyphenyl)ethyl)amino-1-cyclopentene hydrochloride,
(aj) 1-Aza-2,2-dimethylamino-1-cyclopentene hydrochloride,
(ak) 2-Iminopiperidine hydrochloride,
(al) 1-Aza-2-methylamino-1-cyclohexene hydrochloride,
(am) 1-Aza-2-ethylamino-1-cyclohexene hydrochloride,
(an) 1-Aza-2-dimethylamino-1-cyclohexene hydrochloride,
(ao) 2-Imino-3-methylpiperidine hydrochloride,
(ap) 2-Imino-4-methylpiperidine hydrochloride,
(aq) 2-Imino-4-propylpiperidine hydrochloride,
(ar) 2-Imino-4-benzylpiperidine hydrochloride,
(as) 2-Imino-5-methylpiperidine hydrochloride,
(at) 2-Imino-5,5-dimethylpiperidine hydrochloride,
(au) 2-Imino-3,5-dimethylpiperidine hydrochloride,
(av) 1-Aza-2-iminocycloheptane hydrochloride,
(aw) 1-Aza-2-methylamino-1-cycloheptene hydrochloride,
(ax) 1-Aza-2-ethylamino-1-cycloheptene hydrochloride,
(ay) 1-Aza-2-dimethylamino-1-cycloheptene hydrochloride,
(az) 1-Aza-2-benzylamino-1-cycloheptene hydrochloride,
(bb) 1-Aza-2-cyclohexylamino-1-cycloheptene hydrochloride,
(bc) 1-Aza-2-iminocyclooctane hydrochloride,
(bd) 1-Aza-2-methylamino-1-cyclooctene hydrochloride,
(be) 1-Aza-2-ethylamino-1-cyclooctene hydrochloride,
(bf) 1-Aza-2-benzylamino-1-cyclooctene hydrochloride,

(bg) 1-Aza-2-methylamino-1-cyclononene hydrochloride,
(bh) 3,4-Dihydro-2-aminoquinoline hydrochloride,
(bi) 3,4-Dihydro-2-methylaminoquinoline hydrochloride,
(bj) 3,4-Dihydro-2-ethylaminoquinoline hydrochloride,
(bk) 3,4-Dihydro-2-benzylaminoquinoline hydrochloride,
(bl) 3,4-Dihydro-2-cyclohexylaminoquinoline hydrochloride,
(bm) 3,4-Dihydro-2-dimethylaminoquinoline hydrochloride,
(bn) 4-Ethoxycarbonyl-2-imino-piperazine hydrochloride,
(bo) 5-(S)-2-Imino-1-aza-bicyclo(3.3.0)octane,
(bp) 2-Imino-1-aza-bicyclo(4.3.0)nonane,
(bq) *cis*-4,6-Dimethyl-2-imino-piperidine, acetic acid salt,
(br) 2-Imino-4-methyl-piperidine, acetic acid salt,
(bs) 6-Ethyl-2-imino-4-methyl-piperidine, acetic acid salt,
(bt) 4-Imino-5-*cis*-methyl-3-azabicyclo [4.3.0] nonane, hydrochloride,
(bu) *cis*-5-Aminomethyl-4,6-dimethyl-2-imino-piperidine, dihydrochloride,
(bv) *cis*-3-Ethyl-2-imino-4-methyl-piperidine, hydrochloride,
(bw) *cis*-2-Imino-4-methyl-3-n-propyl-piperidine, hydrochloride,
(bx) *cis* and *trans*-2-Imino-4-methyl-piperidine-5-carboxylic acid, acetic acid salt,
(by) *cis* and *trans*2-Imino-4-methyl-piperidine-5-carboxylic acid, methyl ester, acetic acid salt,
(bz) *cis* and *trans*5-Acetamidomethyl-2-imino-4-methyl-piperidine, acetic acid salt,
(cc) 2-Imino-5-n-propyloxy-piperidine, acetic acid salt,
(cd) *cis* and *trans*5-Acetamido-2-imino-4-methyl-piperidine, acetic acid salt,
(ce) 5-Cyclohexyl-2-imino-piperidine, acetic acid salt,

(cf) *cis* and *trans*5-Cyclohexyl-2-imino-4-methyl-piperidine, acetic acid salt,
(cg) 2-Imino-5-trifluoro-piperidine,
(ch) 2-Imino-5-ethyl-4-methylpyrrolidine hydrochloride,
(ci) 2-Imino-4-methylpyrrolidine hydrochloride,
(cj) 2-Imino-4-ethylpyrrolidine hydrochloride,
(ck) 2-Imino-4,5-dimethylpyrrolidine hydrochloride,
(cl) 2-Imino-4-methyl-5-propylpyrrolidine hydrochloride,
(cm) 2-Imino-5-methyl-4-propylpyrrolidine hydrochloride,
(cn) 2-Imino-5-ethyl-4-propylpyrrolidine hydrochloride
(co) 2-Imino-5-ethyl-3-methylpyrrolidine hydrochloride,
(cp) 2-Imino-5,5-dimethylpyrrolidine hydrochloride,
(cq) 2-Imino-3,5,5-trimethylpyrrolidine hydrochloride
(cr) 2-Imino-4-ethyl-5-methylpyrrolidine hydrochloride,
(cs) 2-Imino-4-propylpyrrolidine hydrochloride,
(ct) 2-Imino-4-(2-methyl-ethyl)pyrrolidine hydrochloride,
(cu) 2-Imino-4-phenylpyrrolidine hydrochloride,
(cv) 2-Imino-3,4-dimethylpyrrolidine hydrochloride,
(cw) 2-Imino-4-ethyl-3-methylpyrrolidine hydrochloride,
(cx) 2-Imino-5-methyl-4-propylpyrrolidine hydrochloride,
(cy) 2-Imino-3-azabicyclo(4.3.0)nonane hydrochloride,
(cz) 2-Imino-3-azabicyclo(3.3.0)octane hydrochloride,
(dd) 2-Imino-3-methylpyrrolidine hydrochloride,
(de) 2-Imino-5-methylpyrrolidine hydrochloride,
(df) 2-Imino-5-(S)-acetyloxymethylpyrrolidine hydrochloride,
(dg) 2-Imino-5-(R)-acetyloxymethylpyrrolidine hydrochloride,
(dh) 2-Imino-5-(S)-hydroxymethylpyrrolidine hydrochloride,
(di) 2-Imino-5-(R)-hydroxymethylpyrrolidine hydrochloride,
(dj) 2-Imino-4(S)-methoxy-5(S)-methyl-piperidine, hydrochloride,

(dk) 2-Imino-5(S)-hydroxy-4(S)-methyl-piperidine, hydrochloride,
(dl) 4(S),5(R)-Dimethyl-2-imino-piperidine hydrochloride,
(dm) 4(R),5(S)-Dimethyl-2-imino-piperidine hydrochloride,
(dn) 4(S),5(S)-Dimethyl-2-imino-piperidine hydrochloride,
(do) 4(R),5(R)-Dimethyl-2-imino-piperidine hydrochloride,
(dp) *cis*-Decahydro-2-iminoquinoline hydrochloride,
(dr) *cis*-2-Imino-4-methyl-decahydroquinoline hydrochloride,
(ds) trans-Decahydro-2-iminoquinoline hydrochloride,
(dt) 4(R)-Methyl-2-iminopiperidine hydrochloride,
(du) 4(S)-Methyl-2-iminopiperidine hydrochloride,
(dv) 5(R)-Methyl-2-iminopiperidine hydrochloride,
(dw) 5(S)-Methyl-2-iminopiperidine hydrochloride,
(dx) 3-Iminothiomorpholine hydrochloride,
(dy) 2-Iminopiperazine hydrochloride,
(dz) 2-Imino-decahydro-*cis*-quinoxaline, and
(ee) 2-Imino-decahydro-trans-quinoxaline.

21. A compound of Claim 1 selected from
(aa) 2-Imino-4-methylpyrrolidine hydrochloride,
(ab) 2-Imino-4-ethylpyrrolidine hydrochloride,
(ac) 2-Imino-4,5-dimethylpyrrolidine hydrochloride,
(ad) 2-Imino-4-methyl-5-propylpyrrolidine hydrochloride,
(ae) 2-Imino-5-methyl-4-propylpyrrolidine hydrochloride,
(af)2-Imino-5-ethyl-4-propylpyrrolidine hydrochloride,
(ag) 2-Imino-5-ethyl-3-methylpyrrolidine hydrochloride,
(ah) 2-Imino-5,5-dimethylpyrrolidine hydrochloride,
(ai) 2-Imino-3,5,5-trimethylpyrrolidine hydrochloride,
(aj) 2-Imino-4-ethyl-5-methylpyrrolidine hydrochloride,
(ak) 2-Imino-4-propylpyrrolidine hydrochloride,
(al) 2-Imino-4-(2-methyl-ethyl)pyrrolidine hydrochloride,
(am) 2-Imino-4-phenylpyrrolidine hydrochloride,
(an) 2-Imino-3,4-dimethylpyrrolidine hydrochloride,
(ao) 2-Imino-4-ethyl-3-methylpyrrolidine hydrochloride,

(ap) 2-Imino-5-methyl-4-propylpyrrolidine hydrochloride,
(aq) 2-Imino-3-azabicyclo(4.3.0)nonane hydrochloride,
(ar) 2-Imino-3-azabicyclo(3.3.0)octane hydrochloride,
(as) 2-Imino-3-methylpyrrolidine hydrochloride,
(at) 2-Imino-5-methylpyrrolidine hydrochloride,
(au) 2-Imino-5-(S)-acetyloxymethylpyrrolidine hydrochloride,
(av) 2-Imino-5-(R)-acetyloxymethylpyrrolidine hydrochloride,
(aw) 2-Imino-5-(S)-hydroxymethylpyrrolidine hydrochloride,
(ax) 2-Imino-5-(R)-hydroxymethylpyrrolidine hydrochloride,
(ay) 5-Ethyl-2-imino-4-methyl-piperidine, acetic acid salt,
(az) 2-Imino-4-methyl-5-(1-pentyl)-piperidine, acetic acid salt,
(bb) 4(R)-Methyl-2-iminopiperidine hydrochloride,
(bc) 4(S)-Methyl-2-iminopiperidine hydrochloride,
(bd) 5(R)-Methyl-2-iminopiperidine hydrochloride,
(be) 5(S)-Methyl-2-iminopiperidine hydrochloride,
(bf) 4(S),5(R)-Dimethyl-2-imino-piperidine hydrochloride,
(bg) 4(R),5(S)-Dimethyl-2-imino-piperidine hydrochloride,
(bh) 4(S),5(S)-Dimethyl-2-imino-piperidine hydrochloride,
(bi) 4(R),5(R)-Dimethyl-2-imino-piperidine hydrochloride,
(bj) 2-Imino-5(S)-methoxy-4(S)-methyl-piperidine hydrochloride,
(bk) 2-Imino-5(S)-hydroxy-4(S)-methyl-piperidine hydrochloride,
(bl) 2-Imino-5(S)-methoxy-4(R)-methyl-piperidine hydrochloride,
(bm) 2-Imino-5(S)-hydroxy-4(R)-methyl-piperidine hydrochloride,
(bn) 2-Imino-5(S)-acetyloxy-4(R)-methyl-piperidine hydrochloride,

(bo) 2-Imino-3(S),4(R)-O-isopropylidene-5(R)-acetyloxy-piperidine hydrochloride,
(bp) 2-Imino-3(S),4(R),5(R)-triacetyloxy-piperidine hydrochloride,
(bq) *cis*-Decahydro-2-iminoquinoline hydrochloride,
(br) *trans*-Decahydro-2-iminoquinoline hydrochloride,
(bs) 4(S)-Methyl-4a(S),7a(S)-perhydro-2-imino-1-pyrindine hydrochloride,
(bt) 4(R)-Methyl-4a(R),7a(R)-perhydro-2-imino-1-pyrindine hydrochloride,
(bu) 4(S)-Methyl-4a(S),8a(S)-decahydro-2-iminoquinoline hydrochloride,
(bv) 4(R)-Methyl-4a(R),8a(R)-decahydro-2-iminoquinoline hydrochloride,
(bw) 2-Imino-octahydro-quinolin-6(5H)-one-6-ethylene ketal hydrochloride,
(bx) 2-Imino-octahydro-quinolin-6(5H)-one hydrochloride,
(by) 2-Imino-6-acetyloxy-*cis*-decahydroquinoline hydrochloride,
(bz) 2-Imino-6-hydroxy-*cis*-decahydroquinoline hydrochloride,
(cc) 2-Imino-5-methoxy-cis-perhydro-pyrindene hydrochloride,
(cd) 2-imino-5-hydroxy-cis-perhydro-pyrindene hydrochloride,
(ce) 2-Imino-5-hydroxy-4a-methyl-trans-(4a,8a)-decahydroquinoline hydrochloride,
(cf) 2-Imino-5-fluoro-5-methyl-cis-(4a,8a)-decahydroquinoline hydrochloride,
(cg) 5-Acetoxy-2-imino-cis-(4a,8a)-decahydroquinoline hydrochloride,
(ch) 5-Hydroxy-2-imino-cis-(4a,8a)-decahydroquinoline hydrochloride,
(ci) 2-Imino-octahydroquinolin-7(8H)-one-7-ethylene ketal hydrochloride,
(cj) 2-Imino-octahydro-quinolin-7(8H)-one hydrochloride,

(ck) 7-Acetyloxy-2-imino-trans-(4a,8a)-decahydroquinoline hydrochloride,
(cl) 7-Hydroxy-2-imino-trans-(4a,8a)-decahydroquinoline, acetic acid salt,
(cm) 7-Acetyloxy-2-imino-decahydroquinoline, acetic acid salt,
(cn) 2-Imino-3-Methyl-octahydro-cis-pyrano*[4,3-b]*-pyridine hydrochloride,
(co) 2-Imino-4-methyl-octahydro-pyrano*[4,3-b]*pyridine hydrochloride,
(cp) 2-Imino-4-Methyl-1,3,4,5,7,8-hexahydro-pyrano*[4,3-b]*pyridine, acetic acid salt,
(cq) 2-Imino-1-methyl-piperidine hydrochloride,
(cr) N-(1-Benzyl-2-piperidinylidene)-N'-(phenyl)-urea,
(cs) N-(2-Piperidinylidene)-N'-(phenyl)-urea
(ct)N-[1-(4-Methoxybenzyl)-2-piperidinylidene]-N'-(phenyl)-urea,
(cu) 2-Imino-1-(benzylaminocarbonyl)-piperidine,
(cv) *Cis*-Octahydro-3-imino-2H-1,4-benzoxazine hydrochloride,
(cw) 2-Iminopiperazine hydrochloride,
(cx) 4-Methyl-2-iminopiperazine hydrochloride,
(cy) 2-Imino-decahydro-*cis*-quinoxaline dihydrochloride,
(cz) 2-Imino-decahydro-*trans*-quinoxaline dihydrochloride,
(da) 4-6-Dimethyl-2-imino-piperazine hydrochloride,
(db) 2-Imino-4-methyl-6-(2-methylpropyl)-5-oxo-piperazine hydrochloride.
(dc) 4-Benzyloxycarbonyl-2-imino-(1,2,3,4)tetrahydro-quinoxaline hydrochloride,
(dd) 4-Acetyl-2-imino-(1,2,3,4)tetrahydro-quinoxaline hydrochloride,
(de) 2-Imino-4-methyl-decahydro-*trans*-quinoxaline, acetic acid salt,
(df) 3-Iminothiomorpholine hydrochloride,

(dg) 3-Imino-5-propyl-thiomorpholine,
(dh) 3-Imino-5-methyl-thiomorpholine,
(di) 3-Imino-5-ethyl-thiomorpholine,
(dj) 3-Imino-5-butyl-thiomorpholine,
(dk) 3-Imino-5(S)-(2-methyl propyl)-thiomorpholine,
(dl) 3-Imino-5(R)-(2-methyl propyl)-thiomorpholine,
(dm) 1-(*tert*-Butoxycarbonyl)-hexahydro-3-imino-(1*H*)-1,4-diazepine hydrochloride,
(dn) Hexahydro-2-imino-(1*H*)-1,4-diazepine dihydrochloride,
(do) Hexahydro-2-imino-5-methyl-(1*H*)-1,4-diazepine dihydrochloride.
(dp) Hexahydro-2-imino-4-methyl-(1*H*)-1,4-diazepine hydrochloride,
(dq) 3-Amino-hexahydro-2-imino-(1*H*)-azepine dihydrochloride,
(dr) (*S*)-3-Amino-2-iminopiperidine dihydrochloride,
(ds) Hexahydro-3-imino-1,4-oxazepine hydrochloride,
(dt) Hexahydro-3-imino-1,4-thiazepine hydrochloride,
(du) Hexahydro-3-imino-5-propyl-(1*H*)-1,4-diazepine dihydrochloride,
(dv) Hexahydro-3-imino-5-methyl-(1*H*)-1,4-diazepine dihydrochloride,
(dw) 2-Imino-decahydro-cis-1,4-benzo(e)diazepine dihydrochloride,
(dx) 2-Imino-decahydro-3H-benz(e)azepine hydrochloride,
(dy) Trans-Octahydro-3-imino-2H-1,4-benzthiazine, acetic acid salt,
(dz) 2-Imino-5(6H)-oxa-*cis*-hexahydro-(1H)-quinoline hydrochloride, and
(ea) 2-Imino-4-methyl-5(6H)-oxa-*cis*-hexahydro-(1H)-quinoline hydrochloride.

(eb) (2-Imino-decahydro-cis-3H-benz(e)azepin hydrochloride,
(ec) Trans-Octahydro-3-imino-2H-1,4-benzthiazine, acetic acid salt,
(ed) Cis-Octahydro-3-imino-2H-1,4-benzthiazine, acetic acid salt,
(ee) 2-Imino-5(6H)-oxa-*cis*-hexahydro-(1H)-quinoline hydrochloride,
(ef) 2-Imino-4-methyl-5(6H)-oxa-*cis*-hexahydro-(1H)-quinoline hydrochloride, and
(eg) 2-Imino-decahydro-trans-1,4-benzo(e)diazepine dihydrochloride.

22. A pharmaceutical composition for treating a nitric oxide synthase mediated disease comprising a pharmaceutical carrier and a non-toxic effective amount of the compound accrding to claim 1.

23. A pharmaceutical composition for treating a nitric oxide synthase mediated disease comprising a pharmaceutical carrier and a non-toxic effective amount of the compound accrding to claim 17.

24. A method for inhibiting the activity of nitric oxide synthases comprising administering to a subject suffering from a nitric oxide synthase mediated disease, a non-toxic therapeutically effective amount of the compound of Claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/14812

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/44, 31/445, 31/535, 31/54; C07D 211/56, 273/01, 279/12, 285/15

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	EP, A, 0,155,653 (G.D. SEARLE & CO.) 25 September 1985, formula I on page 4.	1-4, 6-12 and 20-23
X ---- Y	J. Am. Chem. Soc., Volume 108, No. 19, issued 1986, Perrin et al., "Absence of Stereoelectronic Control in Hydrolysis of Cyclic Amidines", pages 5997-6003, see compound 13, page 5998.	1-4, 6-12 and 20-23
X --- Y	J. Chem. Soc. Perkin Trans, issued 1987, Huber et al., "Saturated Heterocyclic. Part 88. Synthesis of New Ring System: Dipyrido-(1,2-*a*:4, 3-*d*) pyrimidin-11-one Derivatives", pages 909-912, see compound 10, page 910.	1-4, 6-12 and 20-30

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 23 FEBRUARY 1996	Date of mailing of the international search report 19 MAR 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Y.N. GUPTA Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/14812

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	J. Heterocyclic Chem. Volume 19, issued July 1982, Kokosi et al., "Nitrogen Bridgehead Compounds. Part 19 (1). Synthesis of Polymethylenepyrimidin-4-ones", pages 909-912, see compound 1, page 909.	1-4, 6-12 and 20-23
X --- Y	Chemical Abstracts, Volume 63, issued 1965, Moehrle, "Synthesis of hydroxylactams by mercury(II)-ethylenediaminetetraacetic acid (EDTA)-dehydrogenatin. VI. Reaction of 1-phenyl-2-(3-methylpiperidino)-1-ethanol", column 11487, Arch. Pharm. , 298(7), pages 440-447, see entire abstract.	1-4, 6-12 and 20-23
X --- Y	Chemical Abstracts, Volume 109, issued 1988, Bodnar et al., "3-Anilino-5, 6-dihydro-1, 4-oxazin-2-one", abstract no. 128921, Zh. Org. Khim., 23(10), pages 2252-2253, see entire abstract.	1-3, 6-8 and 20-23
X --- Y	US, A, 4,054,652 (ROONEY ET AL.) 18 October 1977, column, 1, formula I.	1-3, 6, 10-11, 15-19 and 20-23
X --- Y	Chemical Abstracts, Volume 78, issued 1973, Kummer et al., "5, 6-Dihydro-2H-1, 4-thiazines and -oxazines", abstract no. 111338, DE 2,138,142, see entire abstract.	1-3, 6-8, 10-11, 15-19 and 20-23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/14812

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-12 and 15-24(in part)

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/14812

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/315, 317, 326, 327, 329, 336, 352, 352, 227.5, 227.8, 231.2, 231.5, 235.5, 237.5;
544/56, 59, 60, 62, 98, 106, 111, 120, 122, 162, 165; 546/192, 223, 245, 256, 264, 265, 268

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

514/315, 317, 326, 327, 329, 336, 352, 352, 227.5, 227.8, 231.2, 231.5, 235.5, 237.5;
544/56, 59, 60, 62, 98, 106, 111, 120, 122, 162, 165; 546/192, 223, 245, 256, 264, 265, 268

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

GROUP I, CLAIMS 1-24, DRAWN TO COMPOUNDS, COMPOSITIONS AND METHOD OF USE, WHEN n IS ZERO AND SUBSTITUENT R's ARE NON HETERO OR FIVE MEMBERED HETEROCYCLIC.

GROUP II, CLAIMS 1-24, DRAWN TO COMPOUNDS, COMPOSITIONS AND METHOD OF USE, WHEN n IS ZERO AND SUBSTITUENTS R's ARE PRRIDYL OR ISOQUNOLYL.

GROUP III, CLAIMS 1-24, DRAWN TO COMPOUNDS, COMPOSITIONS AND METHOD OF USE, WHEN n IS ZERO AND SUBSTITUENTS R's ARE PYRAZINYL OR PYRIMIDINYL.

GROUP IV, CLAIMS 1-12 AND 20-24, DRAWN TO COMPOUNDS, COMPOSITIONS AND METHOD OF USE, WHEN n IS ONE AND X IS CARBON.

GROUP V, CLAIMS 1-3, 6, 7, 8, 10, 15 AND 16-24, DRAWN TO COMPOUNDS, COMPOSITIONS AND METHOD OF USE, WHEN n IS ONE AND X IS - O - OR - S - .

GROUP VI, CLAIMS 1-10, 13, 14 AND 17-24, DRAWN TO COMPOUNDS, COMPOSITIONS AND METHOD OF USE, WHEN n IS ONE AND X IS NITROGEN.

GROUP VII, CLAIMS 1-24, DRAWN TO COMPOUNDS, COMPOSITIONS AND METHOD OF USE, WHEN n IS TWO .

GROUP VIII, CLAIMS 1-24, DRAWN TO COMPOUNDS, COMPOSITIONS AND METHODS OF USE, WHEN n IS THREE OR FOUR .

The compounds of inventions I-VIII, are made independently and are used independently. They are independent.

The compounds of the inventions I-VIII are drawn to structurally dissimilar compounds and they are so diverse in nature that a prior art reference anticipating the claims with respect to one member would not render obvious the same claim with respect to another member. If, the oxazoles, thiazoles and imidazoles of Group I, were anticipated, applicants would not acquiesce in objection of any of the Groups II-VIII therover or vice-versa.

Accordingly, the claims are not so linked by a special technical feature within the meaning of PCT Rule 13.2 so as to form a single inventive concept.